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PRELIMINARY OBSERVATIONS ON MENTAL DISTURBANCES OCCURRING IN PATIENTS UNDER THERAPY WITH CORTISONE AND ACTH*

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IT HAS become increasingly apparent, during the past year, that mental disturbances are a not uncommon complication of therapy with cortisone and ACTH. It was initially observed that mild euphoria was frequent in patients undergoing this form of treatment, and more recently a variety of other mental abnormalities have been reported.[1-16] It is intended to describe in this paper a series of patients who developed varying degrees of mental disturbance while under treatment with these agents and to review briefly the possible etiologic factors and theoretical implications involved.

The 10 cases histories to be presented are divided for descriptive purposes into 4 minor and 6 major disturbances. Patients exhibiting only euphoria of slight or moderate degree (that is, short of hypomania) are not included as examples of "mental disturbance" in this paper. This increased joviality and optimism have been seen in nearly all cases treated with cortisone or ACTH at this hospital.

In so far as it is possible, the observations on this unusual group of mental disturbances will be presented at a descriptive level. It is thereby hoped that etiologic assumptions intrinsic to many conventional psychiatric concepts may be avoided. Whenever recourse is made to psychologic abstractions, the latter should be regarded as descriptively analogous to, rather than identical with, corresponding phenomena in previously described psychiatric illness.

CASE REPORTS

Minor Disturbances

CASE 1 (MGH 577758). M. S., a 27-year-old watch-factory worker, was admitted for the third time on March 11, 1950, for advanced, generalized rheumatoid arthritis and duodenal ulcer. For 119 days he received an average of 55.6 mg. of ACTH intramuscularly per day (total dose, 6615 mg.) for his arthritis. Prior to therapy he had been a somewhat unstable person, subject to mild depressive episodes related to his incapacitating illness. His prevailing mood while on ACTH was one of mild euphoria. He described this as follows: "I could laugh all day long; I feel less depressed about my condition, more optimistic."

He suffered periodically for several hours at a time with a peculiar sensation over his forehead, "as if my hair were plastered down over my forehead with something sticky." There was no change in mood, behavior or sensorium in association with these paresthesias except on one occasion. At this time, after 8 weeks on a dosage of 80 mg. per day, he became listless, apathetic and discouraged, coincidentally suffering from particularly severe frontal paresthesias and a sense of heaviness in his head. These symptoms persisted for several days but subsided promptly with reduction of dosage to 60 mg. per day. The patient was discharged on September 23.

CASE 2 (MGH 675504). A. E., a 31-year-old woman, was admitted on September 9, 1949. She underwent prolonged ACTH and cortisone therapy for chronic exfoliative psoriasis and advanced, generalized rheumatoid arthritis. Her past history was not remarkable from a psychiatric point of view; in fact, she had been remarkably stable and uncomplaining despite her distressing illness. During the course of 114 days she received a total of 12,898 mg. of ACTH without significant change in her mental state other than mild euphoria. Two days after the end of therapy she suddenly complained that "Everything is going wrong." She described an intense sensation of heaviness in her head ("a headache without any pain"), transient muscle cramps ("tightening feelings") in her hands and feet and generalized weakness. Holding her hand at the level of her supraorbital ridge, she said: "I feel all hazy and fuzzy above here." At the same time she experienced an ill-defined change in her whole sense of somatic awareness, during which she verbalized for the first time anxiety about the disfiguring effects of her arthritis and psoriasis. On the following day she felt the same and in addition was suffering a vague sense of substernal pressure, attended by marked anxiety and fear of death. By the third day these abnormalities of mental state and sensation had largely cleared.

Subsequently the patient was given orally a total of 24.4 gm. of cortisone in the course of 18 weeks without significant change in her mental state other than slight euphoria, punctuated by brief periods of discouragement in response to fluctuations in her physical well-being. She was discharged on January 16, 1951.

CASE 3 (MGH 636434). E. B., a 24-year-old Army sergeant, was admitted on October 10, 1949, for treatment of Reiter's syndrome, manifested by urethritis, conjunctivitis and arthritis. He was an emotionally stable, intelligent, optimistic man; he had had no psychiatric illness. He received 100 mg. of ACTH (intramuscularly) per day from December 31, 1949, through January 7, 1950. On the 4th day of treatment the patient appeared "depressed" to the ward nurses. On the following day he was evaluated psychiatrically. At that time he recognized that a definite change in his mental state had occurred on the previous day, when he developed

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a "hazy feeling," initially momentary but becoming persistent in the course of the day and continuing throughout the following day. Features of this "hazy feeling" included: disinterest in his usual recreations, vague listlessness, a minor degree of motor and intellectual retardation, slightly impaired capacity for concentration and maintenance of sequential thought during conversation and an ill-defined feeling of detachment from reality. He denied being depressed or anxious but was obviously somewhat apprehensive over the changes that had occurred in his mental state.

On the 3rd day of this disturbance his mental status remained essentially unchanged, except for his being more withdrawn and less responsive in conversation. Early that evening, however, in the course of a few hours he experienced a marked spontaneous diuresis, with coincident clearing of the "hazy feeling." He slept well, but his symptoms had recurred to a moderate degree by morning and persisted during the last day of treatment. Complete recovery had occurred by the next day (January 8).

The occurrence of rather marked changes in fluid balance is to be noted in this case (Fig. 3). His body weight rose 2.5 kg. during the first 4 days of ACTH treatment and then declined to the baseline level during the subsequent 4 days. He was discharged on January 16.

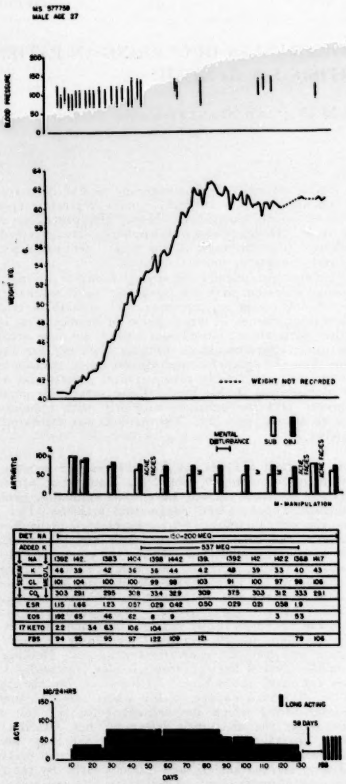


FIGURE 1. *Graphic Representation of Clinical Course, Blood Pressure, Body Weight and ACTH Dosage in Patient M. S.*

In the columns labeled "Arthritis" the observed subjective (SUB.) and objective (OBJ.) responses are recorded. These were judged according to the criteria adopted by the American Rheumatism Association.[12] *The tabulated data include the dietary sodium (Na), the potassium (K) administered, the serum electrolytes (Na, K, Cl and Co2), the sedimentation rates (ESR), the eosinophil counts (EOS), the 17-ketosteroids (17-KETO) and the fasting blood sugar (FBS). All subsequent figures are of the same type.*

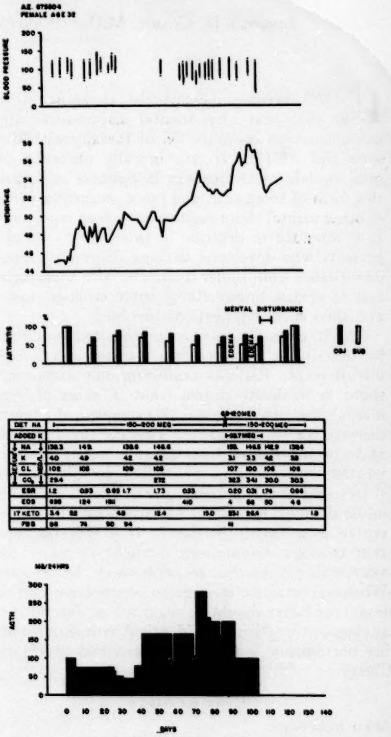
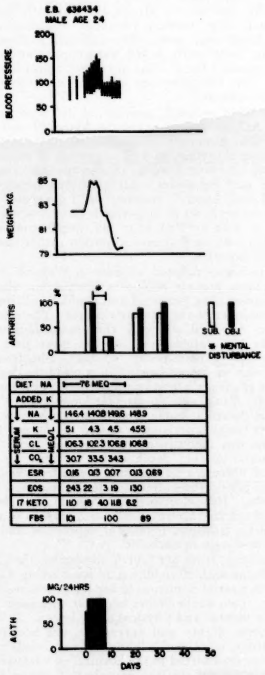


FIGURE 2. *Graphic and Tabulated Data on Patient A. E.*

CASE 4 (MGH 694675). H. R., a 24-year-old college student, was admitted on March 25, 1950, for treatment of Reiter's syndrome, manifested by urethritis, conjunctivitis, keratotic skin lesions and arthritis. He received 2875 mg. of ACTH in the course of 20 days. He was psychiatrically evaluated prior to treatment and found to be a pleasant, highly co-operative, quiet, somewhat introspective but apparently well adjusted man.

His mental status was unremarkable, except for mild euphoria, until the last week of therapy. During that time, coincidentally with an increase in dosage from 160 to 200 mg. per day, a gradual change in his behavior and disposition was noted. He became sarcastic, demanding and less sociable and communicative. On the 18th day of treatment he admitted to feeling abnormal; he described a vague sense of "fullness" or "fogginess" in the frontal portion of his head and "grogginess" in his responses. He denied depression or anxiety. Gradual clearing of these symptoms occurred during



DIET	NA	⟵76 MEQ⟶			
ADDED K					
SERUM MEQ/L	NA	146·4	140·8	146·8	148·9
	K	5·1	4·3	4·5	4·55
	CL	106·3	102·3	106·8	108·8
	CO_2	30·7	33·5	34·3	
ESR		0·16	0·13	0·07	0·13 0·69
EOS		2·43	2·2	3·19	1·30
17 KETO		11·0	11·8	10·40	11·8 8·2
FBS		10·1		10·0	8·9

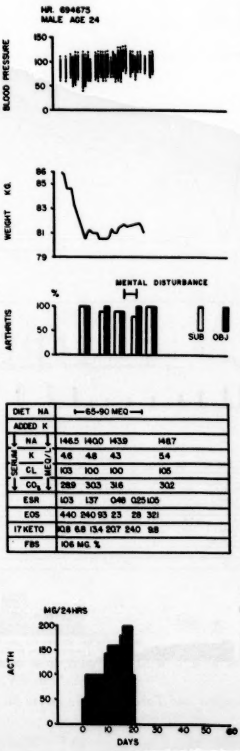
FIGURE 3. *Alterations Observed in Patient E. B. During Eight Days of ACTH Therapy.*

a 3-day period following cessation of treatment. He was discharged on July 5.

Major Disturbances

CASE 5 (MGH 654948). H. S., a 23-year-old housewife, was admitted 5 times (from March, 1949, to December 19, 1950) for treatment of disseminated lupus erythematosus. Prior to therapy the patient was an immature, at times childishly petulant but in general agreeable and stable young woman. Her past history was negative for psychiatric illness.

During her second admission she received an initial course of 1275 mg. of ACTH (intramuscularly) between August 3 and August 17, 1949. The first significant psychic change, other than mild euphoria, occurred on August 14, when she became increasingly loquacious, overactive and restless. On the night of August 16 she fell to the floor kicking, screaming, banging her head against the wall and expressing fears that she was "going mental." The next day she was seen by a psychiatric consultant, who described a number of changes in the patient. He noted a change from her usual compliancy to a demanding, suspicious, antagonistic demeanor; marked distractibility and emotional lability, with alternating frivolity and weeping; slight fragmentation of speech, manifested particularly by incompleteness of sentence structure; and marked motor restlessness. She also evidenced increased concern about her physical disfigurement, in that she insisted on using facial cosmetics and covering her partially bald head with a turban. During this period the patient wrote a letter to her sister, in scrawled, ill-formed sentences, begging that she be saved "from going mental" and grimly describing herself as being "fat as a pig and full of salt water." There



DIET	NA	⟵65-90 MEQ⟶			
ADDED K					
SERUM MEQ/L	NA	146·5	140·0	143·9	146·7
	K	4·6	4·8	4·3	5·4
	CL	103	100	100	105
	CO_2	28·9	30·3	31·6	30·2
ESR		1·03	1·37	0·48	0·25 1·06
EOS		4·40	2·40	9·3	2·8 3·21
17 KETO		10·8	6·8	13·4	20·7 24·0 9·8
FBS		10·6 MG. %			

FIGURE 4. *Alterations Observed in Patient H. R. During Twenty Days' Progressively Increasing Dosage of ACTH.*

was no gross confusion, disorientation or delusional content. After the withdrawal of ACTH on August 18, the patient experienced a marked diuresis, with coincident clearing of her mental symptoms.

On August 22 she was started on a second course of ACTH, which was terminated on November 17. During this time she showed no psychotic manifestations. On September 13 she was for a few hours excessively restless and hypomanic in

mood. However, during October and November she became increasingly difficult to manage because of mounting anxiety over her prognosis, manifested primarily by petulant, insistent questions about ACTH, her future with or without the drug, whether she would receive ACTH in the event of a relapse and so forth. On November 18 the patient, in partial remission from her disease, was allowed to go home.

After discharge her anxieties became even more pronounced. Accordingly, she was admitted to the Psychiatric Service on December 19. At that time she complained of anorexia and insomnia and was preoccupied with the likeli-

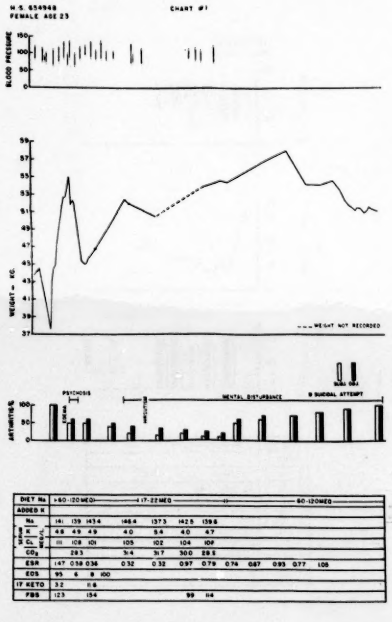


FIGURE 5. *Graphic and Tabulated Data on the Second Hospital Admission of Patient H. S.*

hood of relapse of her disease and whether she would receive ACTH in that event. She appeared depressed, anxious, indecisive and mildly agitated. She showed no psychotic ideation.

She was discharged unchanged on December 24 but was readmitted the next day, having ingested an ounce of iodine in a suicidal attempt. Her mental state was essentially as before. She seemed to express her anxiety over her future through a series of petulant demands, questions, misinterpretations of physicians' statements and threats to go home. After a few weeks exacerbation of her disease necessitated transfer to the Medical Service.

On February 11, 1950, she was once again started on ACTH, and treatment continued through February 31, 1950, on a dosage of 25 mg. per day. Except for some increase in degree of agitation, no significant changes in her mental state occurred until March 1. At that time her course was further complicated by a convulsive seizure. (There was no past history of epilepsy.) Her electroencephalogram, which had previously been normal, showed on March 3 abnormalities in the form of bilateral paroxysmal slow discharges. On March 5, her cerebrospinal-fluid protein was found to be 126 mg. per 100 cc. Bilateral extensor plantar responses were present for a short time after this convulsion. No other abnormal neurologic signs were elicited.

After this convulsive attack the patient's mental status deteriorated. She became paranoid and hostile, and her reality contact was poor. She suffered auditory illusions, interpreting indistinctly heard ward conversations as involving her personal affairs. This psychotic phase had cleared by March 9. On the following day her electroencephalogram remained abnormal.

Because of continued activity of her disease, a fourth course of ACTH was started on March 9 and continued until July 20. A variety of aberrations in mental status occurred during this time, as well as periods of relative normality. During the first 2 weeks of therapy she was apathetic, bewildered and indecisive. All questions produced an immediate "I don't know," "maybe," or "I guess so." She denied being able to read, write or perform elementary calculations. However, it was evident that her intellectual impairment was secondary to marked preoccupation rather than to actual cerebral deterioration.

On April 5 she suffered another convulsive seizure. Bilateral extensor plantar responses were again observed, but on this occasion they persisted and could be elicited throughout the remainder of the patient's course. The electroencephalogram on April 10 was still abnormal. During the next 1½ months the patient was for the most part depressed, withdrawn and in poor reality contact. She frequently expressed a wish to die or begged in a childish singsong voice to be "put to death" by the physicians. She repeated: "I want to die. Can't you execute me somehow? I'm such an ugly girl. If I were at home, I wouldn't know how to do anything." Her facial expression was one of intense fear. Periodically she was incontinent of urine and feces. For a few days she acted out her death wishes by refusing food, with the avowed objective of starving herself. During the last week of this period the patient gradually regained her normal mental state. Her electroencephalogram was reported as normal on April 26. During the final 2 months of this admission, except for transient periods of depression and agitation, her course was not remarkable.

After discharge from her fourth admission, the patient was treated at home with 60 to 90 mg. of long-acting ACTH every other day. A partial remission of her lupus was maintained on this dosage. Two weeks before her final admission, deterioration of both mental and physical state began. At first excessively euphoric, flighty and overactive, she became progressively impulsive, emotionally labile and irrational. On December 19 she was readmitted to the hospital in a frankly psychotic state. In addition she was gravely ill from relapse of her lupus and a complicating *Staphylococcus aureus* abscess with septicemia. She was rambling and obscene in speech, paranoid and regressed in behavior.

During the remainder of her last admission the patient's course was progressively downhill. She received no further ACTH treatment. Varying degrees of confusion and irrationality persisted until death. Three convulsive seizures occurred during the last weeks of her life. She died on February 28, 1951.

This patient presented a particularly difficult problem with regard to evaluation of her mental status. At times she was apparently suffering from a "toxic psychosis," but at other times, as the case history suggests, it was difficult to assay the relative importance of the drug factor as opposed to anxiety and depression related to the threat of her grave illness. She seemed to use a neurotic mechanism

for handling anxiety by displacing the latter on substitute situations created by her petulant questioning and threats to leave the hospital. The mental abnormalities shown during her last admission must obviously be interpreted with caution in view of the coincident severe medical illness.

CASE 6 (MGH 687211). E. M., a 21-year-old girl, was admitted for the first time on December 28, 1949, for treatment of severe rheumatoid arthritis. Her previous psychiatric history revealed a strongly ambivalent attitude toward her parents (her mother in particular) and mild cyclothymia, manifested by brief periods of moodiness and discouragement. While in the hospital she continued, independently of therapy, to have occasional days of mild depression, usually manifested by apathy, tearfulness and pleas for permission to go home.

As a therapeutic trial, the patient was given intramuscularly 100 mg. of desoxycorticosterone glucoside (Ciba) per day from February 5 through March 6, 1950. No significant change in her arthritis was observed. On the last day of this treatment she became tearful, withdrawn, retarded and apathetic. She described herself variously as "lifeless," "without pep" or "as if I needed vitamins." A minor degree of depersonalization and feelings of unreality were present. In addition to suffering anorexia and insomnia, she complained of "fullness" in the head, tinnitus, transient dizziness and blurring of vision. This mental disturbance subsided three days after the cessation of desoxycorticosterone-glucoside treatment.

On March 29 the patient was started on ACTH in a dosage that varied from 40 to 80 mg. per day. Her course was relatively uneventful until May 2, when a capsulotomy was performed on her knees. Four days after the operation she developed persistent nausea and vomiting and also complained of overwhelming drowsiness, intracranial heaviness, blurred vision, apathy and a sense of detachment from reality. She believed that her comprehension of herself and her environment was "blurred." The dose of 60 mg. of ACTH per day was omitted from May 7 through May 11, by which time she had recovered from this episode and ACTH was started again. However, she continued to have, with increasing frequency, periods of depression, crying and insistence on leaving the hospital.

On July 22, 1950, the patient was discharged home on 80 mg. of ACTH per day. So far as can be learned it is probable that because of errors in measuring out the dose the patient received 2 to 3 times the prescribed amount of ACTH during her 4 days at home.

She was readmitted on July 27, in a severely psychotic state. This mental disturbance had begun suddenly on her second day at home, when the patient anxiously told her mother that she was going to die and asked for a priest to administer the last rites. Except for a brief lucid interval on

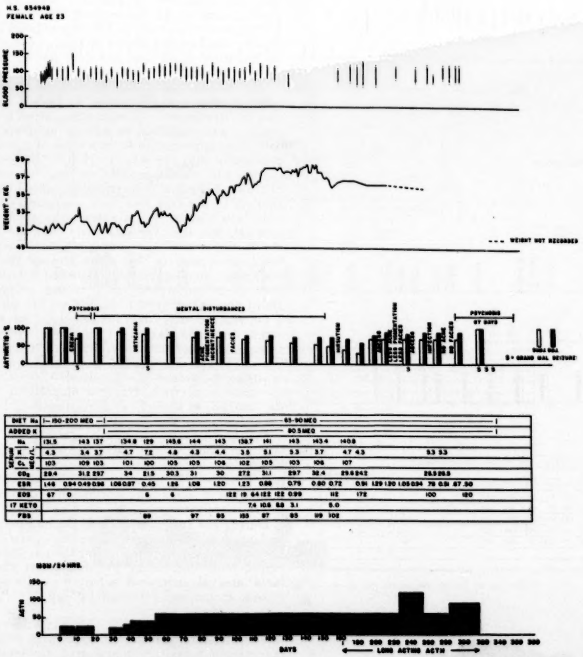


FIGURE 6. *Data on the Third and Fourth Courses of ACTH in Patient H. S.*

the following day, she became progressively distraught and irrational. At the time of admission she was markedly depressed, agitated and withdrawn. Questions about her well-being were answered with a curious sequence of incongruities, in which she insisted that she felt "O. K.," "perfectly well" and "could move" and "do everything" yet that "all was blank," and that she was "empty in the head," "gone crazy" or "dead in the head."

Her speech was rambling, tangential and for the most part unintelligible. She was largely preoccupied with intense

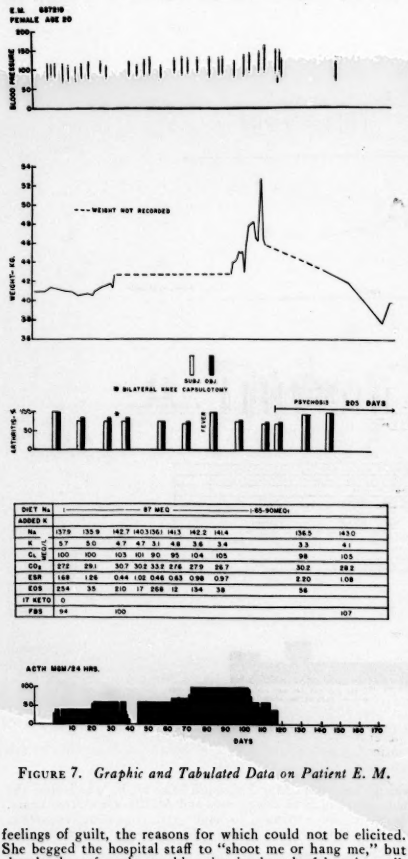


FIGURE 7. *Graphic and Tabulated Data on Patient E. M.*

feelings of guilt, the reasons for which could not be elicited. She begged the hospital staff to "shoot me or hang me," but shortly thereafter she would maintain that she felt quite well. During this week she remained completely irrational, periodically hallucinated, noisy and confused. Urinary incontinence occurred frequently.

On August 23 slight improvement was evident, in that she responded appropriately to routine questions about her arthritis and immediate environment. However, her spontaneous speech remained incoherent, and she was preoccupied and apathetic. A further sign of improvement appeared on August 29, when she expressed awareness that she was suffering a "nervous breakdown." In general, however, she remained withdrawn, making inappropriate responses, and in grossly inadequate reality contact.

During the remainder of her psychosis, only minor changes occurred in her mental state. Periodically she expressed paranoid ideas of depressive quality, that is, that she would be killed or "put away." Hallucinatory experiences continued. Her prevailing mood was one of apathetic depression. For prolonged periods no mental content could be elicited from her except repeated expression of wishes to go home. Toward the end of this period her delusional ideas appeared to cause her less concern. Recovery occurred dramatically in the course of two days and was complete by October 20, 1950. Her subsequent course remained psychiatrically uneventful.

CASE 7 (MGH 384135). J. A., a 20-year-old unmarried girl, was admitted on July 15, 1949, for treatment of advanced, generalized rheumatoid arthritis. Over the course of 122 days she received 13,220 mg. of ACTH intramuscularly. During the last 2½ weeks of this period she was maintained on a dosage of 75 mg. per day, having previously been on dosages as high as 150 mg. per day.

Her clinical course was not remarkable from a psychiatric point of view until December 6, 1949, 2 days before termination of treatment. At that time, after a restless night, the patient was described as having suddenly become "hysterical." She appeared to be in a state of panic and screamed incoherently that she was "in Hell," "the devil is in me," that she was the "chosen one of God" but "possessed of the devil." She also complained distraughtly about the ACTH-induced changes in her face and body configuration. This initial episode lasted about 10 minutes. She then became quiet and rational, but she expressed fears that she might be taken to the "crazy ward." In retrospect one observer believed that for a week prior to this acute episode the patient had been somewhat moody, unduly disturbed by the various medical procedures performed on her and suspiciously concerned about the side-effects of ACTH on her physical appearance.

On the following day she remained for a time emotionally stable but complained of dizziness, fullness in the head, tinnitus and excessive perspiration. After this lucid interval she went into a trance-like state and again described herself as being possessed of the devil. She alternately laughed, screamed and cried. Using a magnifying glass as a mirror, she looked at herself and repeated: "I'm beautiful, I'm beautiful. I'm homely, I'm homely. I don't care."

On the third day the patient was quiet and rational until late afternoon, when she began muttering to herself. She looked into her "mirror" and then became markedly agitated and restless. Her speech consisted of incoherent muttering or explosive screaming, primarily concerning her changed physical appearance.

During the subsequent week she had periods of withdrawal and negativism, agitation, screaming and suicidal threats or brief episodes of repetitive, incoherent speech, but these occurred with decreasing frequency. At the same time, the lucid intervals increased in length until a persistently normal mental status had returned by January 5, 1950.

CASE 8 (MGH 688872). M. M., a 56-year-old housewife, was admitted on January 23, 1950, with advanced, generalized rheumatoid arthritis, complicated by severe iritis. She received 4600 mg. of ACTH intramuscularly in the course of 77 days. The dosage varied from 40 to 80 mg. per day.

Except for mild euphoria, the patient's mental state remained unremarkable during the first 2 months of therapy. However, on July 17 she became suspicious and agitated and expressed fears that she would be rejected by the hospital staff after the completion of her hospitalization or, — even worse, — that ACTH, being a "powerful medicine," might kill her. These concerns appeared to subside with reassurance until 2 weeks later.

On August 1 she developed definite paranoid ideas, claiming that the patients on the ward were discussing her impaired eyesight and that they all knew she was going to go blind. She had frequent crying spells, during which she begged to be taken off ACTH because it would make her go blind. ACTH treatment was terminated 3 days after the onset of this paranoid disorder. When psychiatrically evaluated at this time she appeared drowsy, depressed and somewhat retarded. Her complaints were a heavy feeling in her occiput and forehead and overwhelming fatigue, weakness

and lack of ambition. Her paranoid ideas were only intermittently elicited.

During the next 2 weeks the patient remained depressed, withdrawn, suspicious and defiant. She continued to complain of a sense of intracranial fullness. She repeatedly expressed fear that she would die or go blind. At times these fears were reinforced by paranoid delusions that her case was being discussed over the radio or reported in the newspapers or by auditory hallucinations of a depressive content, such as "Something is going to happen to you; you are going blind." At another time she was preoccupied with fear of day. She has now been maintained on cortisone for 10 months without recurrence of psychiatric complications.

CASE 9 (MGH 572728). W. G., a 62-year-old housewife, was admitted on October 17, 1950, for treatment of severe rheumatoid arthritis. She was immature, self-centered, discursive and affectively shallow. However, her superficial adjustment had been adequate, and there was no previous history of frank psychiatric illness.

Between October 23 and November 4, she received 2775 mg. of cortisone intramuscularly. On November 1 some

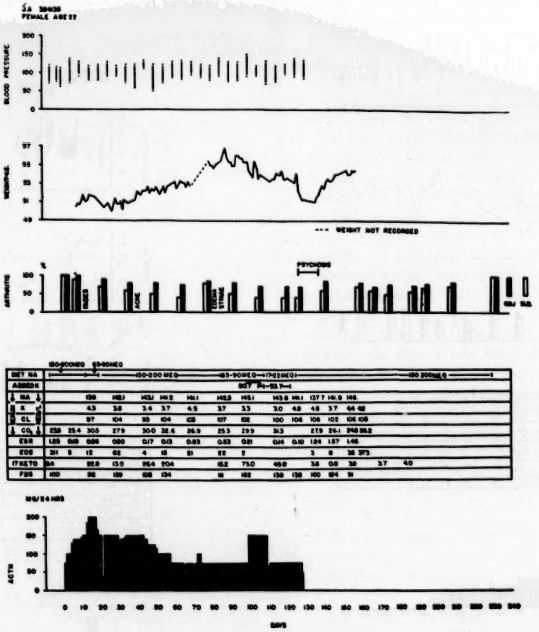


FIGURE 8. *Data on Patient J. A.*

impending death and frequently felt her pulse to ascertain whether she were still alive.

By the end of this 2-week period signs of improvement gradually appeared. At first she became less tearful and depressed, although her paranoid ideas and auditory hallucinations persisted. It is of interest that during the recovery phase depersonalization feelings remained in evidence, in that the patient frequently asked her doctor to tell *her* how she was feeling — as if self-identification remained so impaired that she was unable to appraise her own sensorial experience. As she lost concern with her delusions it was possible to achieve contact with her on more realistic terms. Full recovery occurred gradually over a 2-week period.

Coincidentally with the improvement in her mental state she developed a severe relapse of her arthritis. Accordingly, on September 16 she was started on orally administered cortisone and had received 5.1 gm. by the time of discharge on October 6. With this therapy a good remission of her arthritis occurred. She was discharged on a dosage of 150 mg. per increase in the usual flightiness of her conversation was noticed, but it was 3 days later that definitely abnormal mental symptoms developed.

At that time she appeared depressed and confused, walking restlessly about packing and then unpacking her clothes, but she insisted that she felt "Fine. Swell. The nearest thing to heaven I will ever get." Her speech became progressively unintelligible because of the interpolation of misused words, irrelevancies and tangential associations. Having previously been fastidious, she became slovenly and careless. On November 6 the mental disturbance persisted, but a trace of insight was evident in that she was aware that "Cortisone has affected my mind" — referring to her garbled and inexact speech. Two days later she developed paranoid delusions about the nursing staff and accused herself of greed, selfishness and mistreatment of her family. She was agitated and suspicious; she wanted to leave the hospital but at other times insisted that she was being thrown out.

On November 13 she became progressively apathetic and withdrawn. During the next 2 days she lay motionless in bed; she was incontinent, sleepless, muttering incoherently and negativistic toward those caring for her. She appeared to be experiencing auditory and visual hallucinations and expressed delusions that she was dead, that her husband had died and even that the world had been destroyed. At times she assumed a moribund pose, with flaccid, open mouth and rolled-up eyes.

On the evening of November 15 she suddenly had a brief lucid interval, during which she talked freely in reality terms,

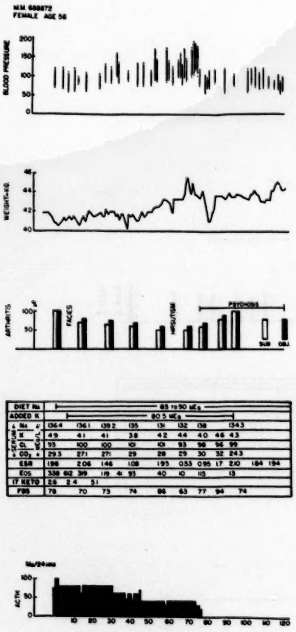


FIGURE 9. *Data on Patient M. M., During and After ACTH Therapy.*

smiled and was in fair contact with her environment. However, after a few hours incoherence, withdrawal and intellectual-affective disorganization recurred. A sample of her speech was as follows: "I thought that I thought that I'd been thinking about thinking all this over. There now, wasn't that a correct answer? I didn't wash my face today. Are you S--?" (her husband).

On November 16 the patient was immobile, affectless, mute and completely unresponsive to her environment. There was a cogwheel-like resistance to passive movement in all extremities. This state clinically resembled catatonic stupor. On the following day she remained immobile and postured but obeyed simple commands. There was a trace of affective response to interpretations by the interviewer directed at her depersonalized state — that is, she became restless and almost spoke, and her lips and hands trembled.

By November 19, although she remained underactive, the patient began to talk incessantly in an agitated manner. Two days later further change was evident, in that for the first time she directed her incoherent communications to the interviewer. On November 22 she was normally oriented, addressed the psychiatrist by name and responded adequately to direct questions, but her spontaneous speech remained obscure. From this time gradual improvement developed in the intelligibility of her speech, but it remained rather stilted, figurative and circumstantial for several weeks after it had become coherent.

During the recovery phase, lucid intervals alternated with periods of apparent perplexity and expression of fragmentary delusions of depressive quality. After December 5 no evidence of psychosis was elicited. However, for several weeks after this time she remained indecisive and diffident and repeatedly sought detailed advice and direction in routine

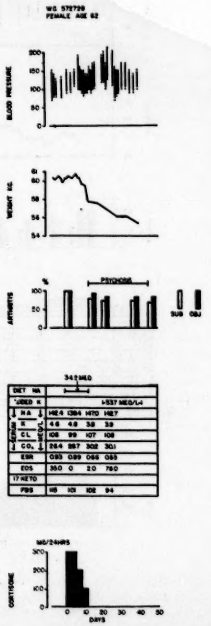


FIGURE 10. *Observations on Patient W. G.*

matters that she had previously managed for herself without difficulty. Security in her previous personality defenses gradually returned.

CASE 10 (MGH 558672). M. W. S., a 49-year-old unmarried businessman, was admitted on October 19, 1950, for treatment of moderately severe rheumatoid arthritis with spondylitis and peripheral joint involvement. He received an average of 230 mg. of cortisone intramuscularly per day from October 24 to November 6. His history revealed that he had been somewhat introverted and socially limited but aggressive, effective and financially successful. About 10 years prior to this admission he had suffered an unduly prolonged grief reaction, with mild depression and seclusiveness, after the suicide of a brother.

The patient's course on cortisone was uneventful except for a period of excessive euphoria on October 30, until November 5. At this time a slowly progressive increase in verbal press and productivity was noted. On November 7 he was emotionally tense, restless and extremely talkative. He used every opportunity to launch into an exhaustive introspective analysis of his past life and its emotional conflicts. His speech was coherent and his reality contact was normal. These psychic changes subsided by November 8.

After a brief lucid period, this hypomanic phase evolved into a severe "schizo-affective" psychosis. On November 12 the patient was extremely overactive, hostile, assaultive and destructive. He showed loss of self-identification (alternately

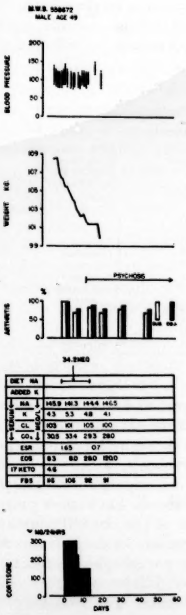


FIGURE 11. *Observations on Patient M. W. S.*

referring to himself as God, his physician or the atomic bomb). During the next month the patient exhibited a bewildering psychotic symptom complex. For the most part he talked in an incoherent, agitated manner of previously suppressed conflicts of his early life, but at other times he was mute and semistuporous. At intervals his behavior was primitive and regressed, consisting of animal-like screaming and raving, urinary and fecal incontinence, masturbation, obscenity, fecal smearing and fetal positions with thumb-sucking. He had visual and auditory hallucinations. For prolonged periods he supplemented his rambling stream of talk with bizarre, symbolic gestures and rituals. Orientation was difficult to evaluate accurately because of his preoccupation and detachment. However, objective observations suggested marked confusion and evident disturbance of his sensorium.

No essential changes occurred in his mental status until December 5, when a brief lucid interval was observed, during which he was in fair contact with his environment and talked relevantly but appeared bewildered. He soon reverted to grossly psychotic behavior.

During the next 3 months brief periods of relative lucidity continued to occur at irregular intervals, but predominantly his mental state remained grossly psychotic. For the most part he was in poor reality contact, incoherent in speech and preoccupied with hallucinatory experiences. At other times he was hostile, agitated and paranoid. However, there was no significant recurrence of the severely regressive behavior described above. Gradually, the periods of rationality increased in frequency and duration. On February 15, 1951, another sign of improvement was evidenced when he momentarily rationalized his psychotic behavior of the previous days as a "bad dream — something I don't want to talk about."

More definite, rapid improvement began on March 7 and continued without the usual relapses for the next 2 weeks. Except for several brief periods of suspiciousness and mild depression, his subsequent course was uneventful. During this recovery phase he was for a time shy, diffident and excessively compliant. As in Case 9, these signs of insecurity gradually cleared.

DISCUSSION

Several general observations, supplementing the case histories presented above, must be made before these mental disturbances are considered in detail. With the possible exceptions described in Case 5, this series of patients showed no evidence of primary or secondary disease involving the central nervous system. Moreover, there were no metabolic changes intrinsic to the primary illness, and no nonhormonal medication was concomitantly given to which a "toxic" mental state might be ascribed.

None of these patients had a prior history of major mental illness. As has been previously noted, minor abnormalities of personality were present in Cases 1, 5, 6 and 10. In general, however, in our series of cases, systematic clinical study revealed no characteristics of premorbid personality that might enable one to anticipate the occurrence or predict the severity or duration of psychiatric com-

TABLE 1. *Dosages in Cases with Minor Disturbances.*

PATIENT	DURATION OF TREATMENT BEFORE ONSET OF PSYCHOSIS	TOTAL DOSE OF ACTH	AVERAGE DOSAGE
	days	*mg.*	*mg./day*
M. S.	119	6,615	55.6
A. E.	114	12,898	113.1
E. B.	8	775	97.0
H. R.	20	2,875	143.7

plications in a given case. Obviously, definitive conclusions cannot be drawn in this regard until more exhaustive pretreatment study has been carried out in a large series of cases.

The clinical and laboratory data relevant to these cases are presented in graphic-tabular form within each case history and in Tables 1 and 2. With the exception of the first and third psychotic episodes of Case 5, all patients who had major disturbances during ACTH therapy had received moderately large doses for over two and one-half months prior

to the onset of mental symptoms. There is no correlation between the severity or duration of the psychoses and the total or average daily dose of ACTH.* On the contrary, Patient A. E., who received the largest total and average doses, suffered only a minor disturbance of two days' duration immediately after cessation of treatment. The two cortisone-treated patients received large doses for only twelve and fourteen days respectively prior to the onset of psychotic symptoms. One of these patients, M. W. S., suffered the most severe and prolonged psychosis in this series. There is also no evident correlation between the rapidity or extent of the therapeutic response to ACTH or cortisone and the occurrence of psychiatric complications. The degree of subjective and objective improvement in each case has been estimated in the respective charts.

The charts of the major cases suggest an approximate coincidence of cessation of therapy and the onset of psychosis. This sequence is misleading, in that it might be regarded as evidence that these mental disturbances represent withdrawal phenomena, such as occur with the barbiturates. In actual fact, only in Patient A. E. did symptoms develop after cessation of treatment. In the major cases, either therapy was omitted because of acute psychotic breakdown or the dosage was reduced and then later omitted as minor untoward changes in mental status anticipated the actual period of psychosis.

It is of some interest that the mental disturbances of Patients M. S., A. E. and E. B. coincided approximately with the peak of their increase in body weight while on ACTH therapy. There is a similar coincidence to be observed in the occurrence of the first psychosis of Patient H. S. and in the psychosis of E. M.

*In regard to the problem of dosage, a recent case (MGH 735279), not included in the present series, deserves mention. This thirty-five-year-old woman received a total of 300 mg. of cortisone (orally) over the course of three days in therapeutic trial for postencephalitic Parkinsonism. After only two days of treatment she developed a depression with auditory hallucinations of paranoid content. Recovery was complete five days after cessation of cortisone. One may speculate that her prior neurologic disease was involved in this extreme susceptibility to psychotic breakdown.

The dietary sodium intake and the amount of potassium administered in the form of potassium chloride prior to and during the mental disturbance are tabulated in Figures 1 to 10. No apparent correlation between the amount of sodium and potassium ingested and the time of onset or the clinical course of the psychosis can be established.

No positive conclusions can be drawn from the laboratory data available on these cases. In particular, there is no constant correlation between the degree of response to ACTH as evidenced by 17-ketosteroid excretion or changes in the serum levels of sodium, potassium, chloride, carbon dioxide or intracellular potassium (as reflected in electrocardiographic changes) and the occurrence of mental disturbances. These data are admittedly not so complete as might be desired, particularly as regards the periods of psychosis, when problems of management seriously hampered laboratory investigation.

TABLE 2. *Dosages in Cases with Major Disturbances.*

PATIENT	DURATION OF TREATMENT	TOTAL DOSE OF HORMONE	AVERAGE DOSAGE	APPROXIMATE DURATION OF MENTAL DISTURBANCES
	days	*mg.*	*mg./day*	*days*
H. S.				
1st course	15	1,275 ACTH	85.0	4
2nd course	87	2,860 ACTH	32.8	?
3rd course	20	460 ACTH	23.0	8 (approx.)
4th course	134	7,380 ACTH	55.0	45 (approx.)
5th course	160	8,940 ACTH	56.0	?
E. M.	121	7,685 ACTH	63.5	8 (severe) 79 (moderately severe)
J. A.	122	13,220 ACTH	108.4	11
M. M.	77	4,600 ACTH	59.8	43
W. G.	12	2,775 cortisone	231.0	32
M. W. S.	14	3,225 cortisone	230.4	150 (approx.)

The case histories have been presented in detail as descriptions of the clinical course or natural history of this unusual form of mental disturbance. In the subsequent paragraphs, an effort at more specific characterization will be made.

The minor cases are primarily of interest in that they represent in mild, discrete form some of the features present in the complex major disturbances. Patient M. S. suffered only periodic paresthesias of his forehead, coincident on one occasion with transient apathy and depression. The "hazy feeling" of Patient E. B. appeared essentially to represent mild depersonalization.† Patient A. E. suffered an acute episode of anxiety and depersonalization feelings. Minor changes in behavior, disposition and intellectual function occurred in Patient H. R. All these patients, as well as several of the major cases, suffered, coincidentally with the mental disturbance, rather characteristic paresthesias of the frontal portion of the head. In addition, Patient A. E. experienced cramps in her ex-

†"Depersonalization" is used here to describe a sense of detachment or strangeness in awareness of one's body image.

tremities and ill-defined chest pains during her period of post-withdrawal disturbance.

The patients with major disturbances exhibited a more complex series of psychic phenomena. In particular, the following abnormalities were observed at one time or another in the 6 patients with major disturbances. Perceptual disorders were frequent and included both illusory and hallucinatory experiences. Disturbances in speech, which were invariably present, varied from mutism to marked press of speech; they also included qualitative abnormalities such as flight of ideas, tangentiality, stereotypy and paralogia. Delusions of depressive, paranoid and grandiose types occurred.

Affective disturbances, also invariably present, varied from depression to hypomania and from apathy to panic; they included ill-defined states that might be described as bewilderment or turmoil. Depersonalization, feelings of unreality and disturbances in perception of the body image were frequently elicited. Intellectual-affective dissociation was evidenced by mere flatness to gross inappropriateness of affect.

Motor disturbances varied from marked overactivity to complete immobility and also included primitive, aggressive behavior and ritualistic acting out. Among the miscellaneous symptoms, anorexia, insomnia, incontinence, distractibility, emotional lability and impaired memory frequently occurred.

The classification of these disorders presents particular difficulty. As is suggested above, they exhibited in their courses most of the phenomenology found in both schizophrenia and affective psychosis. However, in longitudinal view of a given case, these symptoms and mechanisms appeared usually in fragmentary, structureless form and in variable, unpredictable sequence, without the consistency of pattern seen in typical cases of psychosis of spontaneous occurrence. Patient M. M., with her paranoid depression, presented the least variegated course. The other cases more nearly resemble some of the acute schizo-affective disorders, such as panic and turmoil states, or certain cases of combat and post-partum psychosis.

In general, these cases did not exhibit the type of confusion, disorientation and sensorial disturbance usually regarded as characteristic of "toxic deliria," nor was any evidence of defect of recent memory elicited. However, there were numerous instances in which the sensorium of the patient was so overwhelmingly involved with hallucinatory or illusory experiences (especially Patient M. W. S.) or detachment from reality was so marked that the presence or absence of "disorientation" or "confusion" in this strict sense could not be established. This observation suggests inadequate flexibility in the conventional criteria of "toxic psychosis" when applied to this group of mental disorders.

Considerable clinical experience associating psychosis with endocrine disorders is recorded in medical literature. In this regard, thyrotoxicosis, myxedema, Addison's disease, panhypopituitarism and Cushing's disease deserve particular mention. The frequent occurrence of psychosis as a complication of Cushing's disease[18-21] suggests an obvious relation to psychoses induced by cortisone or ACTH. Recovery from this psychosis is known to occur after surgical correction of the overproduction of the adrenocortical hormones.

In addition to these clinical observations, considerable experimental work has been done correlating metabolic changes, — particularly those mediated by the adrenal cortex, — and mental illness. Although a complete review of this literature is not indicated at this point, some observations indicating the general trend deserve mention. In 1938 Gjessing[22] described periodic fluctuations in nitrogen balance in relation to alternating phases of cyclic catatonia. The concept of the hypothalamic–anterior-pituitary–adrenocortical axis as a neurohormonal response pattern has been extensively elaborated by Selye and others.[23, 24] Some studies have been devoted to the metabolic effects of psychologic stress.[25-27] The significance of this latter work in regard to the pathogenesis of psychosis remains undetermined. Promising studies have been carried out on the pattern of sugar and protein metabolism, fluid and electrolyte balance and excretion of adrenocortical hormone in the major psychoses.[28-35] Of particular interest is Altschule's evidence[36] that there is increased excretion of sugar-active hormone in psychotic patients.

As has been suggested earlier in this paper, the reasons for individual susceptibility to mental disturbance during ACTH or cortisone therapy remain unknown. Similarly, the precise pathogenetic mechanisms involved in these abnormalities of cerebral function are not yet determined. We believe that further study of these problems by extensive psychologic, neurologic and metabolic observations during both the premorbid and morbid states should be carried out. Such observations may afford a new insight into the etiology of spontaneously occurring psychoses.

Management

Clinical experience is not yet sufficient to outline definite contraindications to ACTH or cortisone therapy from a psychiatric point of view. We have on general principles advised caution in the use of these agents in patients with disease involving the central nervous system or with a past history of major psychiatric illness. It is hoped that further study may add substance to these assumptions.

The premonitory symptoms of these mental disturbances are variable and at times subtle in onset. Close observation must be maintained for their early detection. Paresthesias in the frontal portion of the head (usually described as a sense of heaviness, fullness or fuzziness), insomnia and increasing

restlessness, agitation or psychomotor activity are particularly to be noted. However, in some cases the expression of delusional ideas or the sudden appearance of psychotic behavior may be initial symptoms of the psychiatric complications.

All cases of psychosis in this series received only supportive care on the psychiatric or medical wards of the Massachusetts General Hospital. Efforts were made to maintain continuity of management during the psychotic period by the resident and staff physicians who had initially treated the patient. Complete recovery occurred spontaneously in all cases. The pattern of recovery in the prolonged cases showed the occurrence of lucid intervals of gradually increasing frequency and duration until a normal mental state was consistently present.

A difficult decision arises when severe mental symptoms complicate therapy with ACTH or cortisone of critical illness, such as disseminated lupus erythematosus. Whether or not recovery from these mental disturbances might occur despite continuance of treatment is a question that unfortunately cannot be answered on the basis of our experience. During her fourth course of ACTH, Patient H. S. suffered a psychotic episode that cleared despite continuance of ACTH in lower dosage. However, the fact that this episode dated from a convulsive seizure introduces the possibility that this disturbance may have been of postictal character, thus vitiating the significance of recovery despite continuance of ACTH. Among the minor cases, the disturbance of Patient M. S. cleared with reduction of the dose of ACTH, and his course remained subsequently uneventful. It is of some interest that Patients M. M. and A. E., whose courses on ACTH have been described, have both subsequently received large oral doses of cortisone without recurrence of psychiatric complications. If untoward mental symptoms develop during therapy, it is perhaps advisable to reduce the dosage for a period of several days, continue close psychiatric observation and withdraw hormonal treatment if the mental condition continues to deteriorate.

Summary

A series of 4 minor and 6 major cases of mental disturbance occurring in the course of therapy with ACTH and cortisone has been presented in detail.

Relevant clinical and laboratory observations on these cases have been outlined.

An attempt has been made to characterize the clinical course and symptomatology of these disorders.

Possible implications of the occurrence of hormonally induced psychosis for future investigation of major psychiatric illness have been suggested.

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ERYTHEMA MULTIFORME BULLOSUM (STEVENS-JOHNSON SYNDROME)*

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A NUMBER of reports have appeared in the literature in recent years on the condition known as the Stevens-Johnson syndrome. The numerous descriptive names attached to its multiple manifestations have caused considerable confusion. There is still controversy concerning whether it is similar to Hebra's "erythema exudativum multiforme" (1886). Less commonly used names are "ectodermose erosive pluriorificialis" (of the French authors), dermatostomatitis, erythema multiforme bullosum, "eruptive fever"[1] and so forth.

Ginandes[2] in 1935 suggested that cases be divided into two groups: severe — erythema exudativum multiforme (Stevens-Johnson), and mild — erythema exudarivum multiforme (Hebra).

Thomas[3] classified them as "erythema exudativum multiforme," "major" and "minor." More recently Robinson[4] suggested that these groups of eruptions of undetermined etiology be classified as the "ocular-mucous membrane syndrome." He grouped together such variants as erythema multiforme, Stevens-Johnson disease, ectodermose erosive pluriorificialis, Behçet's disease and Reiter's disease.

This syndrome is still comparatively little known among physicians in general. The seasonal incidence in 90 per cent of the cases is stated to be in the months from January to June[1] and in the fall.[5] It is more common in males[3, 6] in the first and second decades. It is definitely not in the "pediatric sphere," as stated by Murphy.[6] There is a predilection for the white race.[5] However, of 7 patients seen by the authors in the past two years, only 2 were white. In brief, this is an acute, febrile, sometimes fulminating systemic disease, which may last from a few days to several weeks. Lesions involving the mucous membranes (conjunctivas and orifices), skin and respiratory tract appear almost immediately. Not all systems are necessarily involved in all cases. The skin lesions may be macular, papular, annular, iris-type or vesiculobullous. Involvement of the respiratory tract may be manifested by an acute bronchitis or an atypical pneumonitis[7]; these are said to be the most formidable aspects of the disease.[3] Most serious of all are the lesions of the eye — conjunctivitis, keratitis, iritis, uveitis, hemorrhagic neuroretinitis and so forth, which may result in total blindness. Though usually a self-limiting disease, it has caused a number of deaths. There is a definite tendency to recurrence.

The etiology of the disease is unknown. Viral origin has been suspected. Finland and his coworkers[7] obtained a positive complement-fixation test for psittacosis in 2 cases and a positive cold agglutination in 1. Human foot-and-mouth disease has been implicated.[8] The theory that the disease has an allergic etiology appears to be the most tenable. It is considered to be a sensitivity reaction to either drugs or bacterial products. The relation to sulfonamide therapy is more than coincidental, as is borne out by many reports.[9-11] Many other drugs have been implicated.[5]

We wish to report the results of the treatment of 2 such cases with pituitary adrenocorticotrophin (ACTH) and cortisone.

CASE REPORTS

CASE 1. A. G., a 22-year-old Negro woman, was admitted to the University Hospital on May 29, 1950, with ulcerative lesions of the mouth and pharynx and a purpuric eruption of the extremities. The patient had been well until approximately 1 month prior to admission, when she noted joint pain, swelling of the ankles and a vaginal discharge. She was seen by a private physician, whose diagnosis was probable septic arthritis (gonococcal) secondary to pelvic infection. At this time there was a profuse vaginal discharge, and the physician prescribed sulfadiazine. Approximately 5 days prior to admission the patient began to have fever and chills, and on the next day she noted dark-brown and black spots on the skin of her legs and on her soles and palms. She consulted a second physician, who noted an acute pharyngitis and a skin eruption and diagnosed her illness as scarlet fever. Accordingly, he administered a repository type of penicillin, 600,000 units intramuscularly, and prescribed 1 gm. of sulfathiazole every 4 hours. Because of failure to improve, the patient came to the emergency room of the University Hospital. Her past history was noncontributory.

Physical examination at the time of admission revealed a well developed, well nourished, acutely ill woman with a temperature of 102.6°F. There were many purpuric spots over the extremities and a hemorrhagic ulcerative cheilitis and stomatitis. The skin revealed many dark, almost black necrotic patches of iris-shaped lesions over the dorsal aspects of the extremities and an occasional bulla containing clear serous fluid and numerous dark papular lesions. The size of the black iris lesions varied from 0.2 cm. to 1.5 cm. in diameter. These lesions were seen predominantly over the extremities distal to the elbows and knees. There were also true purpuric lesions of the palms measuring 0.5 to 1.0 cm. in diameter and coalescing in some areas to form lesions of 2 to 3 cm. in diameter. The mouth and lips showed an extensive hemorrhagic ulceration involving the hard and soft palates and the buccal mucosa. There was slight bleeding from the mucosal lesions.

There was a generalized lymphadenopathy, and the eyes showed an acute, diffuse conjunctivitis. The neck was not stiff. The heart size was within normal limits, and a soft systolic murmur was heard at the apex. The cardiac rate was 142. The blood pressure was 112/75, and the respirations were 26. The lungs were clear. The abdomen was scaphoid but otherwise negative. Pelvic examination revealed slight tenderness in the left adnexas.

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Examination of the blood revealed a white-cell count of 8650, with 82 per cent polymorphonuclear leukocytes. Spinal puncture revealed only 5 leukocytes per cubic mm. and a negative test for globulin (Pandy, Ross-Jones).

A provisional diagnosis of bacteremia was made; blood cultures were obtained, and the patient was started on antibacterial therapy — both penicillin and sulfadiazine. Cultures were inoculated with spinal fluid and fluid from an unruptured bulla and from the exudate of the lip lesions.

On the following day the temperature was 101.6°F. and the patient was clinically unimproved. At this time the diagnosis was revised to toxic erythema multiforme bullosum (Stevens-Johnson syndrome), and it was thought that sulfonamide therapy might have been the responsible agent. Accordingly, sulfonamide therapy was stopped and treatment with penicillin and oral and parenteral administration of fluids was continued. A chest film revealed slight pulmonary congestion. The blood Kahn test was negative. The white-cell count was 8300, with 80 per cent polymorphonuclear leukocytes and 1 per cent eosinophils. The hemoglobin was 11 gm. (Sahli). The prothrombin time was prolonged to 24.4 seconds (control, 16.1 seconds), and vitamin K therapy was instituted. The patient was also started on Pyribenzamine, 50 mg. three times daily; wet boric-acid compresses were applied to the eyes and lips.

Cultures of spinal fluid, skin bullae and blood were sterile. The cultures of the lip lesions showed staphylococci. On the 8th hospital day the prothrombin time had fallen to 17.5 seconds (control, 15.1 seconds); the patient became disoriented and excited and wandered about the ward in a confused state. The clinical course was progressively downhill, the temperature elevation ranging to about 101°F. daily; the patient became apathetic, lethargic and finally semistuporous. On the next day the stupor deepened, and the patient was unresponsive to painful stimuli. The white-cell count on this date (the 9th) was 7450, with 60 per cent polymorphonuclear leukocytes, 20 per cent eosinophils and a hemoglobin of 10.1 gm. On the 10th day she was moribund and comatose, and it was believed that she was near death. ACTH was started on the 10th day, 25 mg. intramuscularly every 6 hours for 24 hours, then 25 mg. every 8 hours. On the next day the white-cell count was 15,100, with 84 per cent polymorphonuclear leukocytes. Within 48 hours after institution of therapy with ACTH, the temperature fell to normal, where it remained through the remainder of hospitalization; consciousness and orientation returned as rapidly. ACTH was reduced to 25 mg. every 12 hours of the 4th day of this treatment. By the fifth day of ACTH therapy the patient could sit up alone and was mentally clear. ACTH was discontinued after 6 days of therapy, a total dose of 475 mg. having been given.

The ulcerations of the lips were slow to heal, but bleeding responded well to local applications of Gelfoam and Bacitracin ointment. By the 21st day the patient was able to eat soft food. On the 28th hospital day an electrocardiogram showed only sinus tachycardia. A biopsy of one of the purpuric skin lesions showed "slight perivascular lymphocytic infiltration of the corium." Gradually the skin lesions healed by desquamation and with pigmentation. The patient was discharged on the 36th hospital day, with subsiding cheilitis. When she subsequently visited the out-patient department complete healing of all lesions was seen, but areas of patchy pigmentation of the skin remained.

CASE 2. B.S., a 14-year-old Negro boy, was admitted to the University Hospital on March 24, 1951, with the chief complaint of eruption of the skin of the face, mouth and body. The onset of the present illness had occurred 5 days prior to admission, with the appearance of irregular scattered lesions over the face, the skin of the trunk and extremities and the genitalia. In 48 hours lesions had developed on the mouth, tongue and palate that interfered with eating and swallowing.

Three days prior to admission the patient had received (as an out patient) therapy for pruritus and conjunctivitis, consisting of antihistamine medications, Benadryl and Thephorin ointment and a sulfonamide. He denied the use of any medication for 2 months prior to the onset of the present illness.

The patient stated that he had had similar episodes on four preceding occasions, the last having occurred 3 years previously. His history was otherwise noncontributory.

Physical examination showed a temperature of 99.6°F.; positive findings concerned the skin and the lymph system, which showed a general adenopathy. Numerous raised circular lesions were scattered over the face and extremities. Few lesions were noted on the trunk. The lesions varied in size from 0.3 to 2.5 cm. in diameter and were of varying ages. Some were vesicular, some bullous and some iris-shaped. There were ulcerated lesions on the palate and buccal mucosa. The penis showed swelling and redness of the prepuce, which could not be retracted. Numerous iris-shaped lesions and some bullous ones were seen on the shaft and prepuce, as well as on the scrotum. The extremities showed such lesions also.

Examination of the blood showed a red-cell count of 5,970,000 per cu. mm.; a white-cell count of 4850, with 41 per cent polymorphonuclear leukocytes, 42 per cent lymphocytes, 12 per cent monocytes and 5 per cent eosinophils and a hemoglobin of 17.8 gm. The urine was negative for albumin and sugar; it was acid in reaction and showed 4 to 8 leukocytes per high-power field. The blood Kahn test was negative. The fasting blood sugar was 89 mg. and the nonprotein nitrogen 36 mg. per cent. The sulfonamide blood level was 3.5 mg. per cent. A phenolsulfonphthalein test showed 30 per cent of the dye excreted in 15 minutes and 20 per cent in 1 hour, a total of 50 per cent.

A diagnosis of erythema multiforme bullosum was made. Procaine penicillin therapy for the secondary infection was started and hydrogen-peroxide mouthwash and a liquid diet prescribed. On the following day the penicillin was discontinued. There had been little change in the patient's condition. Cortisone acetate (intramuscularly) was started — 100 mg. every 8 hours on the 1st day, 100 mg. every 12 hours on the 2nd day and 100 mg. daily thereafter. Within 24 hours after the start of cortisone therapy the lesions had diminished markedly. The patient regained the ability to swallow and to eat solid food. In 48 hours nearly all the lesions were dry and many had completely cleared. In 96 hours all the lesions had cleared. The patient was discharged 5 days after admission.

He was readmitted on May 11, 1951, with a recurrence of the skin eruption. He again denied the use of any medication prior to or during the present illness. Examination revealed vesicular and bullous lesions of the face, chest and upper extremities. There were several vesicles on the hard palate and on the inner surface of the lower lip. No lesions were present on the penis or scrotum. There were several enlarged submental and submaxillary lymph nodes. The temperature was 99.2°F. The rest of the examination was not noteworthy.

Laboratory examination revealed a leukopenia (a white-cell count of 4600), with 69 per cent polymorphonuclear leukocytes; the rest of the blood picture was within normal limits. Urinalysis was not remarkable; the specific gravity was 1.026. The blood Kahn test was negative and the blood sugar and nonprotein nitrogen were normal.

A diagnosis of erythema multiforme bullosum was made, and the patient was started on ACTH, 25 mg. intramuscularly every 6 hours, bed rest and a regular diet. During ACTH therapy there was very slight improvement of some lesions. However, the patient developed a new lesion on the upper lip during treatment. After 4 days of therapy with 25 mg. of ACTH every 6 hours it was thought that progress was not satisfactory; in view of the patient's previous dramatic clearing with cortisone, therapy was changed from ACTH to cortisone acetate, 100 mg. orally every 12 hours on the first day, then 100 mg. daily. Within 48 hours after the start of cortisone therapy the arm lesions had almost entirely cleared. The oral lesions had also cleared, and for the first time since its appearance the new lesion over the upper lip had regressed. There was complete clearing by the 5th day of cortisone therapy, and the patient was discharged on the 10th hospital day. Of incidental interest was the rise in blood pressure from 120/80 before cortisone was instituted to 150/100 during treatment.

DISCUSSION

As with any disease of undetermined etiology, treatment of erythema exudativum multiforme and its various manifestations is unsatisfactory and mainly symptomatic. The efficacy of specific

therapy is difficult to evaluate in a disease that is generally self-limited and in which drug idiosyncrasy must be considered.

Sulfonamides and penicillin were of little or no benefit in most cases.[8, 12, 13] Recently several reports[8, 14, 15] have appeared describing aureomycin therapy, but response to the drug has not been specific.

Lever and Talbott[16] obtained encouraging results with adrenocortical hormone in bullous dermatitis. In addition to the 2 cases reported herewith a similar dramatic response to ACTH and cortisone was obtained by Biederman and Wammock [17] in another patient. Although we realize that the number of cases is too small to warrant definite conclusions, we believe that the results obtained were favorable enough to warrant further extensive trial of these hormones in this syndrome.

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PROBLEMS OF ISCHEMIA OF THE LOWER EXTREMITY*

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AMONG the problems of an aging population, ischemia of the lower extremities ranks high in importance. Until recently it was thought that peripheral ischemia due to this disease was an irreversible process. Now, thanks to early investigations in this field, the value of lumbar sympathectomy has been adequately demonstrated. It is no longer justifiable to assume that a thigh amputation is the only treatment for failing circulation to the lower extremities. Linton[1] has pointed out that this operation offers "the best protection that can be given the patient against the development of gangrene in old age." There are now more than 25,000,000 persons over the age of fifty in the United States; many of these will eventually need help because of failing circulation to the legs.

Arterial obstruction may be of slow evolution, accompanied by a gradual enlargement of the preexisting collateral channels. It is recognized that despite marked arteriosclerotic changes in the major vessels the collateral and small vessels may be unusually free of disease. These collateral vessels are constantly subject to the vasoconstrictor influences of the sympathetic nervous system as temperature changes, exercise or the "borrowing and lending" of blood by other tissues of the body make their demands for a change in the total flow through the tissues of the legs. This vasoconstrictor tone may serve as a handicap to the local tissues if their chief source of nourishment has been depleted by arteriosclerosis in the major arteries; it is this spasm of the collateral vessels that under certain conditions may make the difference between viable and gangrenous toes. Recognition of the warning signs of this impending disaster may enable the alert physician to spare his patient a thigh amputation. Fortunately, intermittent claudication may call the attention of the patient, — and later, of his physician, — to this insidious change. If the vasospastic component is a factor, lumbar sympathectomy will increase the circulation to the extremities.

Cold, painful feet, an infection about a toe or intermittent claudication may first bring a patient to his physician. Rubor, rest pain and skin changes are late developments, and every effort should be made to treat failure of the peripheral circulation before these findings appear. The challenge to the physician then resolves itself into two component parts: first, the need for a reasonably early diagnosis and second, the selection for lumbar sympathectomy of only those patients who have a vasospastic component. At the present there is no infallible test for the selection of patients for this operation. There seems to be general agreement that severe

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cerebral, cardiac or renal arteriosclerosis, intractable rest pain and marked atrophic changes of the skin of the feet are all contraindications for operation. In addition to the above, Edwards[2] has pointed out that in his experience gangrene proximal to the toes has been an additional contraindication for the operation.

One must consider not only the extremity but the entire cardiovascular status. Allen, Barker and Hines[3] found that 54.6 per cent of 240 patients with peripheral arteriosclerosis, associated with symptoms, died within three years after their first visit to the Mayo Clinic. Although arteriosclerosis may be patchy in its development, it is still a generalized disease. Various tests have been utilized for the selection of suitable cases for operation. In general, satisfactory results may be expected in any patient with a cold, moist foot. At Duke University, patients have been given an injection of 50 mg. of priscoline. If there is a prolongation in the venous filling time, sympathectomy is not advised. By and large, a lumbar sympathetic block gives one a fairly accurate idea of the results to be obtained from operation if there is a satisfactory rise in skin temperature. All authors seem to agree, however, that there are occasional cases in which results after sympathectomy have been most satisfactory although the preliminary block with novocain showed no rise in skin temperature or subjective improvement in the legs. When one considers the variations in the lumbar sympathetic chain and the technical difficulties that occasionally arise in the precisely placed injection of the anesthetic solution, it is not surprising to read of such inconsistencies.

In 1948, Thomason and Moretz[4] reported a method of continuous lumbar sympathetic blocks before the American College of Surgeons. They used a spinal catheter inserted beneath the transverse process of the second lumbar vertebra; by this means they were able to flood the gutter with novocain and pencillin every three hours. It seemed to us that if one were to rely at all on lumbar blocks in the selection of patients, the utilization of such continuous blocks would give the physician an opportunity not only to study the effect on skin temperature but to test the functional capacity of the leg as well. Our experience with this form of continuous lumbar sympathetic block has been most satisfactory; on several occasions when we had observed no response from a single block, a continuous block in the same patient demonstrated an increase in exercise tolerance and a rise in skin temperature. Within the past year we have used a small plastic tube in place of the more expensive spinal catheter. We have also employed the continuous caudal block, as described by Hinson and Southworth in 1942.

Although numerous approaches have been described for a lumbar sympathectomy, we prefer the transverse incision across the flank to the outer edge of the rectus muscle at the level of the umbilicus. In the present series 73 such operations have been performed, but only 50 cases have been followed to form the basis for this report. None of the flank muscles were divided, except in 1 case in which, because of the large size of the patient, it was necessary to make a 1-inch incision across the internal oblique muscle. The exposure gained by splitting the oblique and transversalis muscles is improved by dissecting a thin layer of fascia off the fibers of the external oblique muscle. This investing membrane anchors the muscle fibers to its surface and limits exposure and retraction of the muscle. It is of equal importance to separate the oblique and transversalis muscles from each other before splitting their fibers. Relaxation of the iliopsoas muscle is gained by flexing the uppermost leg at the hip and knee with the patient in a lateral position.

The lumbar sympathetic chain is one of the most variable portions of the sympathetic nervous system. The number of ganglia in any given chain may vary from 1 to 5, fused ganglia being counted as 1. Fusion of 2 or more ganglia is not uncommon. Livingston[5] is quoted as saying: "It is almost absurd to state that the second, third, and fourth ganglia are removed. What is meant is that the surgeon removed as much of the chain as he could conveniently get at as near the usual location of the first lumbar ganglia to a point where it passed beneath the iliac vessels into the pelvis." Cowley and Yeager[6] have suggested that perhaps for adequate denervation all the sympathetic tissues should be removed covering the second and third lumbar vertebras. All wounds in the present series were closed in layers with nothing stronger than interrupted sutures of No. 70 cotton; this attests to the natural strength of this physiologic incision. There were no wound infections, no hernias and no deaths. All patients were ambulant in eighteen to twenty-four hours and were usually ready for discharge with a healed wound on the fifth postoperative day. If a bilateral operation was performed, the second stage was usually carried out five or six days later and the patient discharged on the fifth day after the second operation.

Coller,[7] of the University of Michigan, reported 1 death and 5 wound infections in 63 cases. It is interesting to note that 4 out of 5 of these infections occurred in cases with ulcerations or gangrene of the feet, a fact that indicates the hazard of performing this operation in the presence of active infection in the lower extremity.

Paradoxical Gangrene

This paper would not be complete without a word about the so-called paradoxical gangrene, the form of gangrene that develops rapidly after sympathectomy. This has been thought to be due to the opening of small arteriovenous shunts that sidetrack the blood from the terminal capillaries. This hypothesis remains to be proved, as some sympathec-

tomies are performed in the presence of an arterial thrombosis whose later propagation, rather than the lumbar sympathectomy itself, may explain the development of such gangrene. In the present series only 1 such case was observed; in this case it was possible to demonstrate at a later amputation that the femoral artery was thrombosed to at least a mid-thigh level.

Vasodilating Drugs

The use of vasodilating drugs has the disadvantage of causing widespread vasodilatation, which in turn causes a fall in the peripheral resistance of the extremity. Learmonth, of Edinburgh, stated two years ago: "To secure the best results in treatment I believe that it is absolutely essential for the vasodilatation to be *continuous and prolonged;* it is difficult if not impossible to achieve this by the action of drugs. . . . The area in which constrictor tonus is released is a limited one. Over the remainder of the body constrictor tonus maintains the peripheral resistance at normal values, with the result that the blood pressure is maintained at its normal value."[8]

Additional Causes of Peripheral Ischemia

Although arteriosclerosis is the commonest cause of ischemia of the lower extremities, there are other conditions in which the vasospastic component is so prominent that lumbar sympathectomy is indicated. Thromboangiitis obliterans and causalgia are two of the more important. In the latter, a local injury may serve as an irritative focus and set up a reflex disturbance in the sympathetic nervous system, which may require sympathetic denervation for relief. The tragedy of this condition is that the underlying physiology of the disturbance is sometimes not recognized. Many of these patients may be labeled as psychoneurotics. Causalgia should always be considered in patients who have cold, painful lower extremities, often associated with edema, and who give an antecedent history of trauma. X-ray films may show an osteoporosis. The relief following lumbar sympathetic block can be dramatic.

Thromboangiitis obliterans is still a relatively rare cause of failure of peripheral circulation in the extremities. Here again, if the endarteritis is not too extensive and the vasospastic component is prominent, lumbar sympathectomy is of value in the treatment of this disease.

Although the operation has been advocated in the handling of the postphlebitic leg in some sections of the country, the writer has not been impressed by the high incidence of chronic arteriovasospasm in this distressing condition. During the past five years only 3 patients out of several hundred with postphlebitic sequelae have been advised to have a lumbar sympathectomy, and only 2 have submitted to the operation. In these damaged legs many factors contribute to the disturbed physiology, and it is sometimes difficult to evaluate accurately the role of each. The symptoms of the postphlebitic leg are primarily due to chronic venous stasis, and it is only occasionally that this symptom complex is complicated by an associated arteriovasospasm in the chronic stage. Unless the surgeon is reconciled to the need of frequent explanations to a dissatisfied patient, he should select his candidates for a lumbar sympathectomy in this group with extreme care. Recurrent ulcerations on a cold, cyanotic, sweaty leg, in which the indicated surgery on the venous tree has already been effectively carried out, is probably the only indication for a lumbar sympathectomy in the postphlebitic leg.

Massive venous thrombosis is an extremely rare condition. Veal[9] has reported 11 cases in which he pointed out the absence of vasospasm as an etiologic factor. The only case seen by the author was characterized by a sudden onset of pain, edema and cyanosis during hospitalization for anticoagulant therapy in the treatment of a thrombophlebitis of the deep veins of the lower leg. The prothrombin time was 32.8 seconds on the day of the onset of the acute symptoms. In this case there was a dramatic onset of swelling, cyanosis and "a feeling as if the leg would burst." Elevation of the leg, with a continuous lumbar sympathetic block, had no effect on the course of the disease. The extremity rapidly became gangrenous, and a low-thigh amputation was carried out. The pathologist's report indicated patency of all arteries, with complete thrombosis of the venous tree. In several instances Veal has successfully treated this complication by elevating the lower extremity on pillows so that the knee is flexed at a right angle. At the present time we must consider that massive venous thrombosis is not an indication for a lumbar sympathectomy.

Results of Operation

The author has reviewed 50 personal cases of lumbar sympathectomy performed during the past three years for the conditions described above. Whereas a long follow-up is necessary to evaluate the end results in many surgical conditions, the results of lumbar sympathectomy are usually evident at once. If there is a rise in the skin temperatures and an increase in exercise tolerance, and if intractable pain disappears or impending gangrene is aborted, obviously a good result has been obtained. The follow-up study of these cases has disclosed one especially interesting fact. Over a period of months there has been a demonstrated increase in the oscillometric index at the ankle that was not evident immediately after operation. Although this has not occurred in the majority of cases, it has appeared frequently enough to deserve mention. The literature contains many references to the increase of collateral circulation in the denervated lower extremity, but little emphasis has been placed

on the effect on the major arterial trunks that may occur in some of these cases of peripheral arteriosclerosis. If the patient noticed an increase in skin temperature and exercise tolerance the result was classified as good, indicating that there had been an increase in the peripheral circulation. If he was relieved of pain but noticed little improvement in skin temperature or exercise tolerance he was classified as improved. Patients who later underwent major amputations or who noticed no subjective improvement were classified as not improved.

In the series studied 83 per cent were classified as good, 10 per cent as improved and 7 per cent as not improved. It must be emphasized that this series represents an earnest attempt to select only those patients who were expected to benefit from the operation and that the poor results represent an error in judgment.

Discussion

It now appears that lumbar sympathectomy may be accepted as an extremely valuable aid in the treatment of the ischemic extremity. In the light of present knowledge, we must recognize the limitations of the operation and select the candidates with extreme care if we are to avoid needless surgery. Routine lumbar sympathectomy on unselected series has been given adequate trial and is no longer justifiable.

At the present time the chief problem in this field concerns the indications and contraindications for operation. More information is needed to aid the surgeon in a wise selection of these cases. Edwards[2] has found that necrosis proximal to the toes and extensive visceral disease are contraindications for operation. These situations represent advanced states of the disease, however, and are easily recognized. In our experience continuous lumbar sympathetic block has been more helpful than the single injection in measuring exercise tolerance and relief of vasospasm.

At the present time it appears that the following are definite indications for lumbar sympathectomy: peripheral ischemia associated with a cold, moist foot; causalgia; intermittent claudication with palpable popliteal pulses; superficial necrosis of the toes with demonstrable vasospasm; and peripheral ischemia that responds to a sympathetic block as indicated by a rise in skin temperature and an increase in exercise tolerance. Contraindications are: deep gangrene proximal to the toes; advanced arteriosclerosis in patients with a limited life expectancy; advanced atrophy of the skin and subcutaneous tissues of the feet with an absence of filling of the superficial veins and rapid blanching on elevation; and severe pain at rest. Equivocal indications are: physical signs of ischemia without symptoms (Kirschner[10] has raised the question of prophylactic sympathectomy in this group); intermittent claudication, a dry foot and marked rubor in patients who show no improvement with lumbar sympathetic block; and superficial necrosis limited to the toes with no pulses palpable below the femoral in patients who show no improvement with lumbar sympathetic block. It seems to the writer that there is a need of additional information concerning this equivocal group. As more reports become available, we may be helped in the selection of patients who might be expected to receive benefit from the operation.

Lumbar sympathectomy should now be more widely performed by general surgeons. In some hospitals the operation has been delegated to the neurosurgeon, but now that the indications for lumbar sympathectomy are becoming clearer the general surgeon should accept this responsibility, as the associated care of ulcerating and gangrenous lesions, together with the indicated amputations, more logically falls within their province.

If continued progress is to be made in the prevention of the late results of peripheral ischemia of the lower extremities, signs of the disease must be detected at an early stage and an adequate lumbar sympathectomy performed where indicated.

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FOREIGN-BODY PERFORATIONS OF THE GASTROINTESTINAL TRACT*

A Report of Six Cases

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FOREIGN-BODY injuries of the gastrointestinal tract constitute an important challenge to the surgeon. They are frequent in occurrence,[1-7] varied in symptomatology and treacherous in their close simulation of other disease patterns.

This report presents 6 such cases observed within fourteen months on a 50-bed general surgical ward.

CASE REPORTS

CASE 1. M. C., a 59-year-old woman, entered the hospital complaining of increasing constipation of 3 months' duration, accompanied by tenesmus, lower-abdominal cramps, occasional bright-red blood at stool and a 25-lb. weight loss. Physical examination disclosed nothing remarkable except for slight left-lower-quadrant tenderness. Laboratory data was noncontributory. Barium-enema examination revealed an obstructive lesion of the rectosigmoid; the roentgenologic interpretation was probable carcinoma of the upper rectum or rectosigmoid.

During excision the rectal lesion appeared to be a large carcinoma and was described as a "hard, irregular mass which completely surrounded and infiltrated the upper and mid rectum, and was firmly attached to the bladder anteriorly." The pathologist's gross diagnosis was scirrhous carcinoma. Microscopical sections of the lesion showed only diffuse fibrosis. Further gross dissection revealed a 4-cm. spicule of wood in a sinus tract within the perirectal mass.

CASE 2. K. G., a 63-year-old man, entered the hospital with the chief complaint of crampy periumbilical pain of 24 hours' duration associated with malaise, anorexia and constipation. Physical examination revealed an obese, elderly man in acute distress. The abdomen was moderately distended, with periumbilical tenderness. The rectal temperature was 101°F. The white-cell count was 13,000. Peritoneal aspiration recovered turbid, purulent fluid.

Laparotomy revealed diffuse fibrinopurulent peritonitis and "the appendix was involved in a diffuse inflammatory reaction but was obviously not the origin of it." After extensive search and dissection of matted intestinal loops, a toothpick was found projecting from a loop of small bowel. The foreign body was readily removed and the perforation closed. The patient's postoperative course was uneventful.

CASE 3. S. M., a 59-year-old woman, entered the hospital with the chief complaint of 4 weeks' moderate epigastric distress. The illness began with upper-abdominal pain, radiating to the back, and associated with anorexia, watery stools, marked thirst and polyuria, but was not severe enough to prevent her from continuing work as a domestic. There was no appreciable weight loss. Five days before admission she developed chills and fever. Pre-admission roentgenography suggested a large pancreatic tumor. Physical examination revealed an elderly, obese woman in moderate distress. A tender epigastric mass was felt. The rectal temperature was 102°F. The white-cell count was 34,000. The blood sugar was 400 mg. per 100 cc.; the urine was brick red in color.

The provisional diagnosis was upper-abdominal carcinoma with septic necrosis, and diabetes. Immediate therapy was instituted to correct severe dehydration and to control the diabetes. On the 2nd hospital day the patient suddenly went into shock with coma. The abdominal mass was aspirated and pus was obtained. Incision and drainage revealed a large subhepatic abscess, with a small fishbone in its center. On the 5th postoperative day, circulatory collapse recurred, followed by a cerebral hemorrhage or thrombosis, and the patient died. Post-mortem examination failed to reveal the site of perforation.

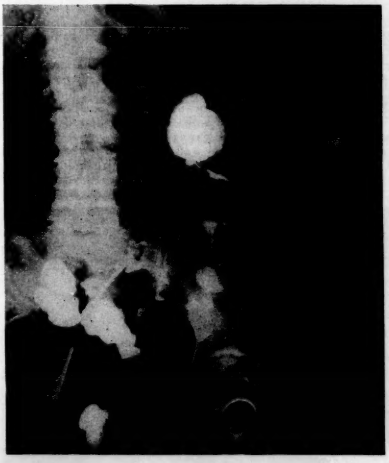

FIGURE 1. *Abdominal Film in Case 4, Made With Lipiodol, Demonstrating the Sinus Tract and Part of the Retroperitoneal-Abscess Cavity.*

Barium in the rectum obscures a portion of the tract.

CASE 4. A. M., a 59-year-old woman, entered the hospital in coma with a large perianal abscess. After drainage of the abscess, roentgenographic studies revealed a long sinus tract

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extending into the left retroperitoneal area about the kidney and under the diaphragm (Fig. 1). No connection with bowel was demonstrated. After a stormy 3-month illness she recovered and was discharged with persisting flank (counter-drainage) and perineal sinuses. Ten months later she developed a second perianal mass and was readmitted. Examination revealed a large abscess in the buttock at the site of the previous infection. When drained, the abscess was found to have a toothpick in its cavity. Prompt and complete recovery followed.

Comment. The etiology of this nearly fatal infection was not discovered during a three-month hospital stay. The site of perforation of the bowel was never demonstrated. However, a short side branch of the sinus tract was visualized radiologically near the rectosigmoid, thus suggesting that the original perforation was in that region.

CASE 5. J. F., a 64-year-old man, entered the hospital complaining of rectal pain of 48 hours' duration. On the day before admission he felt pain on defecation and the protrusion of a small mass from the anus.

Physical examination revealed an elderly man in moderate distress. Rectal examination elicited marked tenderness and spasm, and a firm object was palpated. This proved to be a sharp fishbone, 3 cm. in length, projecting through the mucosa of the anus into a mass resembling an external hemorrhoid. After its removal the patient recovered rapidly.

CASE 6. N. Q., a 63-year-old man, entered the hospital complaining of periumbilical pain of 2½ weeks' duration. He had had no bowel movement for 4 days prior to admission. Physical examination revealed a well developed, well nourished man. An orange-sized, firm, immobile, tender midline epigastric mass was felt. The rectal temperature was 101°F. The white-cell count was 11,300. A "scout film" of the abdomen was suggestive of incomplete intestinal obstruction.

After a provisional diagnosis of strangulated epigastric hernia was made, the mass was explored and was found to be an abscess in the abdominal wall, deep to the rectus sheath. After drainage the patient recovered. Roentgenologic studies of large and small bowel failed to reveal the origin of the infection. One month after discharge a 2-cm. fishbone was removed from a persistent abdominal-wall sinus. The wound healed promptly. Five months later the patient was readmitted for repair of a hernia at the site of drainage. The transverse colon was found to be adherent to the abdominal wall in this region.

Comment. In this case the site of perforation of the bowel, though not proved, appears to have been the transverse colon.

DISCUSSION

In these 6 cases of foreign-body perforation of the gastrointestinal tract the correct diagnosis was not made or even seriously considered. None of the patients gave a history of previously swallowing a foreign body. Each case closely simulated some other common surgical disorder. Only one of the 6 had an acute onset. Roentgenography failed to reveal the foreign body in all cases.

It is noteworthy that 4 of the 6 cases involved the large bowel, which, in reported data, is the site of perforation in only 1 of every 6 cases.[3, 4]

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MASSACHUSETTS PHYSICIANS ART ASSOCIATION

2. *Mamie Fredericks*

(Art Committee's Bronze Medal, Century Association of New York, 1951)

Study in Oil of An Assistant Probation Officer for Colored Children at West Palm Beach, by

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MEDICAL PROGRESS

DIGITALIS POISONING AND ITS TREATMENT

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THERE is no more fitting introduction to the subject of digitalis intoxication than William Withering's description, in his "An Account of the Foxglove," of a visit to a traveling Yorkshire tradesman:

> I found him incessantly vomiting, his vision indistinct, his pulse forty in a minute. Upon enquiry, it came out that his wife had stewed a large handful of green foxglove leaves in a half pint of water and given him the liquor which he drank at one draught. . .this good woman knew the medicine of her country, but not the dose of it, for the husband narrowly escaped with his life.

Although it has been almost three centuries since Withering described the benefits of the proper use of digitalis and the dangers of overdosage, much confusion still exists concerning the indications for its use and the necessary cautions to be observed. The relatively recent introduction of a large number of purified highly potent cardioactive glycosides has made the accumulation of a new experience with their use mandatory. The subject of digitalis poisoning is, therefore, as pertinent in our day as it was in Withering's.

Despite its historic usage in the treatment of the failing heart, the fundamental action of digitalis is still incompletely understood. Several recent reviews have summarized the physicochemical data dealing with the nature of congestive heart failure and its treatment with the digitalis preparations.[1, 2] The cardioactivity of the digitalis group of drugs is due to their content of glycosides, which somehow enter the myocardial muscle cell and are then split into inert sugars and "aglycones," or "genins," which possess definite cardiac potency. The nature of the basic complex linking aglycone and heart muscle is not known, although actomyosin is probably involved in the union. The bulk of evidence seems to indicate that the primary effect of digitalis is an increase in cardiac work without comparable changes in oxygen consumption, probably accomplished by an improvement in the ability of the actomyosin fibril to utilize phosphate-bond energy.

There are several characteristic results of this action of digitalis on the heart. Rhythmicity in the sinus node is depressed, whereas that in the atrioventricular node is heightened. Conductivity in the junctional tissue is slowed, as is seen most vividly in the response of patients with auricular fibrillation and a rapid ventricular rate. This slowing has been ascribed in part to vagal stimulation,[3] since it can be abolished by atropine or vagal section; further digitalization apparently invokes an extravagal mechanism, as procedures on the vagus nerve are no longer successful in speeding the heart rate. Conduction in the myocardial fibrils is affected in varying ways, but the over-all improvement in the circulatory dynamics results in an increase in conductivity. Finally, although it is commonly said to be prolonged, the refractory period is actually shortened, according to Wedd.[4]

Muscle-fiber length decreases, and the heart becomes a smaller pump. In the normal heart the cardiac output falls. In the dilated failing heart, muscle fibers reach a more nearly optimal length under digitalis stimulation; the heart decreases in size, but cardiac output increases with all the characteristic familiar phenomena accompanying recompensation.[5-7] Lastly, myocardial irritability may be increased, with the subsequent appearance of ectopic rhythms — a result usually observed with toxic rather than therapeutic doses of the drug.

The rational use of the active principles of digitalis is a consequence of these physiologic properties. These drugs are indicated in congestive heart failure, whatever the type and structural defect or accompanying arrhythmia. Digitalis should be used in the presence of such manifestations of limited cardiac reserve as protodiastolic gallop rhythm and paroxysmal nocturnal dyspnea. It is the treatment of choice in the paroxysmal auricular arrhythmias. Digitalis has been suggested prophylactically to aid the inhibition of cardiac hypertrophy and delay the appearance of cardiac insufficiency in patients with hypertension or valvular disease.[8] Indeed, the studies of Harrison,[9, 10] Herrmann[11] and Meyers[12, 13] and their associates on the chemical content of normal, hypertrophied and failing hearts seem to provide the experimental rationale for this prophylaxis.

Misinterpretation of the action of the digitalis drugs has led to their use in conditions that have been classed as "erroneous indications"[14]; these warrant mention. The presence of a heart murmur *per se* is not an indication for glycoside therapy, nor is hypertension or the coronary-artery syndromes uncomplicated by cardiac insufficiency, in the general opinion.[15, 16] Digitalization is not recommended routinely before operation in patients without cardiac failure, serious heart strain or auricular arrhythmias. There is no indication for these drugs in neurocirculatory asthenia, periph-

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eral circulatory collapse or constrictive pericarditis in the absence of auricular fibrillation or flutter. Cardiac arrhythmias with dangerous sequelae may be precipitated by their use in acute rheumatic carditis.[17] Digitalis is ineffective in thyrotoxicosis in the absence of congestive failure; recent laboratory studies point to its toxic potentialities in this condition.[18]

Digitalis is contraindicated when adequate indications are lacking or when there is evidence of intoxication with the drug. Idiosyncrasy or true allergy is unusual and outside the experience of many cardiologists.[4] Digitalis may induce Adams–Stokes seizures in the presence of transient complete heart block by further slowing the ventricular rate.[7] Unless the block is due to digitalis, it may be employed when heart failure complicates this conduction disorder.[4, 7] It is almost universally thought to be contraindicated in the presence of paroxysmal ventricular tachycardia[4, 7, 19-22] unless heart failure occurs and quinidine is ineffective in terminating the attack.[7] Schemm[23] suggests that this arrhythmia may call for more, rather than less, digitalis to forestall the development of heart failure and restore myocardial efficiency. In the presence of carotid-sinus hypersensitivity, digitalis action on the vagus nerve may induce attacks.[7]

The digitalis preparations must be used cautiously in combination with certain other drugs. The effects of salts of calcium on the heart are well known; they are also mediated by vagal and extravagal means.[27, 28] Many experimental data suggest that calcium and digitalis may be additive or synergistic, in their cardiac activity,[29-41] although Smith, Winkler and Hoff[32] believe that a comparison of the fatal dose and serum concentration of calcium at death in control and digitalized animals does not justify this assumption. Deaths have, however, been reported as following the intravenous use of calcium in previously digitalized patients,[33] and it has been stated "that it is wiser to abstain from intravenous injection of calcium in any patient who is receiving digitalis since the margin of safety is narrow, and the toxic effects can neither be foreseen nor successfully treated."[34]

Ephedrine has also been said to be contraindicated when digitalis is being used, as there is some evidence that the activity of the two may be additive.[35]

Although aware of the experimental[36, 37] and clinical evidence[38, 39] supporting the use of quinidine in the treatment of digitalis-induced arrhythmias, Gold and his co-workers[40] point out the dangers inherent in this combination. Their studies indicate that there is no synergism between the sinus slowing and depression of auriculoventricular conduction produced by the vagal action of digitalis and the tendency of quinidine to cause similar effects by direct cardiac depression. The auricle becomes quite sensitive to depression by quinidine in the digitalized subject; hence doses that produce only acceleration in controls may lead to auricular standstill during the auricular arrhythmias of digitalis poisoning. It is Gold's opinion that since the effect of the joint use of these drugs is unpredictable quinidine should not be used or should be employed with extreme caution in the digitalized patient.

These, then, are the situations in which Richard Cabot is said to have stated that digitalis may be needed and useful, or not needed and dangerous. It can readily be seen that poisoning may occur in the presence of contraindications or in the absence of indications.[41] The more perplexing problems arise in the presence of frank decompensation where digitalis, if rationally employed, may prove life-saving. In this situation, in which digitalis may be needed as well as dangerous, toxicity occurs most frequently.

There is some evidence that the incidence of toxicity may vary with the functional status of the patient; a wide margin exists between toxic and therapeutic doses of digitalis in the less severe grades of failure, seen in ambulatory patients, whereas in the advanced decompensation of the severely ill the margin may be dangerously narrow.[42] There is also indication that the basic heart rhythm may also be of consequence, since bigeminal rhythm, for example, has been found to be more frequent in patients with auricular fibrillation,[43, 44] and ventricular fibrillation is easily induced in patients subject to transient bouts of this arrhythmia prior to the use of digitalis.[45]

Vigorous diuresis due to concomitant use of the mercurials,[39, 44, 46] the ion-exchange resins[47-49] and the artificial kidney[48, 49] may induce toxicity in patients on a fixed maintenance dose of digitalis or in those in whom the drug is being withdrawn,[48, 49] presumably by mobilization of digitalis from edematous tissues and serous cavities,[46, 50] although recent evidence indicates a specific electrolyte disturbance as responsible.[47-49]

Much confusion has resulted from the retention of the term "cat unit" in speaking about doses of digitalis preparations. The "cat-unit" potency of digitalis leaf, for example, is not comparable to the "cat-unit" potency of the pure glycosides[14]; to use these drugs interchangeably on the assumption that they are comparable may prove fatal. In addition, there have been changes in U.S.P. standardization from one edition to another, and there may even be a wide variation in the biologic potency of drugs with identical U.S.P. unitage.[3] It is obvious that the clinician has little recourse but to rely on only one or two preparations with which he is thoroughly familiar in the routine treatment of cardiac failure.[41]

The introduction of the so-called "pure" glycosides of digitalis has been held responsible for the great increase in the incidence of digitalis toxicity.[7, 41, 51-54] Although the therapeutic ratios for the

glycosides are quite similar (that is, when the maintenance dose is doubled toxicity occurs in about the same number of patients),[55] digitoxin, in particular, has been incriminated because of its slow cumulative action, prolonged excretion and the absence of many of the classic warnings of impending toxicity with its use.[51-56] Recent studies with gitalin, a water-soluble fraction of digitalis purpura, have demonstrated a higher margin of safety with its use than with any other preparation, as well as an excretion rate between that of digitoxin and digoxin. This happy combination may make gitalin the glycoside of choice for routine management, if further trial is corroborative.[57]

Misunderstanding of the data of Gold[3] has led to the indiscriminate use of a single fixed oral digitalizing dose of the glycosides as well as a rigid maintenance dose, without regard for the size and condition of the patient[53, 56, 58]; serious consequences have ensued.[58] It is to be emphasized that treatment must be individualized to deal with the situation at hand and not governed by hard and fast "rules of thumb."

Unfortunately, signs and symptoms of digitalis intoxication may be obscured by concomitant disease, — especially of the gastrointestinal tract,[41] — or may be completely lacking, even in the face of profound disturbances of cardiac rhythm.[39, 59] The latter situation has been largely a consequence of the use of the pure glycosides in general and of digitoxin in particular.[51-56] For example, Moody, in his analysis of 43 cases of digitalis toxicity,[56] found that only 23 patients complained of symptoms attributable to the drug and only 23 patients showed signs of toxicity; only 3 patients had both signs and symptoms simultaneously. Even the classic digitalis effects on the ST segment and T wave of the electrocardiogram may be absent in as many as two thirds of the cases of overt intoxication.[51, 60]

Burwell and Hendrix[41] have assessed the role of the foregoing factors in a study of 35 cases of digitalis poisoning observed over a seven-year period; in many patients several causes were operative. In the largest number (74.3 per cent) warnings of poisoning were ignored; in others (38.6 per cent) there was no rational explanation for the use of digitalis. Other poisonings were attributable to excessive use of digitalis to the neglect of other measures (22.9 per cent), self-medication by the patient (14.3 per cent), error in prescription by the physician (8.6 per cent) and concurrent disease that obscured the clinical evidence of toxicity (11.4 per cent).

The detection of digitalis toxicity in its earliest stages may be extremely difficult, as neither signs nor symptoms may be obvious.[51-56, 59, 60] However, the appearance of any of the classic signs or symptoms of digitalis poisoning described so well by Withering, in the absence of other demonstrable cause, should call for immediate withdrawal of the drug. Further, although ST-segment and T-wave alterations in the serial electrocardiogram may be an expression of therapeutic effect,[41, 62] these changes may also be considered signs indicating extreme caution in the further use of the drug,[60-65] as their appearance in laboratory animals corresponds to the absorption of from 20 to 30 per cent of a minimum lethal dose.[65] Naturally, the development of any of the various ectopic rhythms and conduction disorders to be described should indicate immediate withdrawal of all digitalis, as well as the use of one or several of the positive measures to be mentioned.

In the laboratory animal the first manifestations of digitalis intoxication correspond to very strong vagal stimulation and are reflected by the development of bradycardia, cardiac irregularity, diastolic pauses and an idioventricular rhythm. Next, muscular irritability is increased with attendant acceleration of the rate; the ventricles function with a rapid rhythm independent of that of the auricles, and extrasystoles appear with waxing and waning of the pulse. Complex irregularities occur and are succeeded by superficial ineffective cardiac contractions, as first the auricles and then the ventricles pass into fibrillation.[66] In these animals focal areas of myocardial necrosis and fibrosis have been observed; these are especially common in the subendocardium and the posterior papillary muscle of the left ventricle.[67-69] Severe coronary vasoconstriction[70, 71] or a shortening of the period of coronary filling[71] may be at fault. These lesions are common in older animals[67] and in the presence of experimentally induced hyperthyroidism[18]; they are rarely seen in normal animals who have received therapeutic doses of digitalis.[67, 68, 71] Digitalis poisoning in man may be manifested by many of the rhythmic disorders seen in the laboratory animal, but similar pathologic lesions have not been demonstrated.[72]

Digitalis and its glycosides have been responsible for the production of every known type of arrhythmia and conduction disorder. As Katz states, "digitalis can cause any type of change in the electrocardiogram. In its imitative ability it is to the electrocardiogram what syphilis is to internal medicine."[60] These disturbances occur,[41, 63] although rather infrequently, in persons without organic heart disease.[63]

Digitalis has caused sinus arrest[54, 73] and sinoauricular block.[51, 56] Auricular premature contractions may precede the development of paroxysmal auricular fibrillation,[17, 41, 51, 54, 74-76] auricular flutter[51, 73, 75, 77] or tachycardia.[51, 53, 58, 63, 73, 74, 78, 79] These paroxysmal auricular disorders may result in all degrees of heart block[17, 41, 51-54, 63, 74, 78-80] in the presence of a depressed auriculoventricular bundle — perhaps because of the inability of the poisoned junctional tissue to transmit the shower of impulses reaching it.[17, 22] Nodal tachycardia occurs frequently with digitalis overdosage.[4, 81] Digitalis ranks second only to organic coronary-artery disease as a cause of complete heart block.[80] In man, as well as in laboratory animals, complete

dissociation of auricles and ventricles with idioventricular complexes[41, 52, 56, 73, 82-85] heralds the absorption of a high percentage of the lethal dose of the drug.[65]

On the other hand, although ventricular extrasystoles appear in animals only after 50 to 80 per cent of the minimum lethal dose has been given,[65] in man they are the commonest and often the earliest expression of digitalis intoxication, sometimes appearing after one or two doses of the drug.[41, 51-54, 86-91] Extrasystoles may occur frequently and produce bigeminal or trigeminal rhythm.[41, 43, 44, 51-54, 56, 74, 86-91] Most cases of bigeminal rhythm of digitalis origin are due to ventricular extrasystolic coupling in patients with auricular fibrillation; bigeminy not caused by the drug may equally well be of nodal, auricular or ventricular origin, and the preceding cardiac arrhythmia is as often a normal sinus arrhythmia as any other type.[43, 44] Bigeminal rhythm is said to be produced by digitalis only in the presence of a diseased myocardium[43, 91] and may be the only manifestation of toxicity.[59]

The digitalis preparations are by far the greatest single cause of paroxysmal ventricular tachycardia [52-54, 59, 74, 76, 78, 88, 92-98] in the presence of severe myocardial damage, often with auricular flutter or fibrillation.[76, 93, 95] This acceleration is often misinterpreted as an expression of further decompensation or of the development of auricular flutter, both requiring more, rather than less, digitalis, with the subsequent production of irreversible damage.[52-59] The onset of such a rapid heart rate, with bidirectional ventricular complexes in the electrocardiogram, is a poor prognostic sign.[92, 93, 95] Marvin states that "the implications are clear. Any significant increase in heart rate without an obvious physiologic cause, in a patient who is receiving digitalis, or any apparent failure of digitalis to slow the fibrillating heart, should be regarded with suspicion."[59]

Fatalities may follow the use of digitalis and are commonly attributed to the development of ventricular fibrillation,[45, 51, 54, 59, 89, 99, 100] although electrocardiographic proof has been offered in only 6 cases.[100] Wegria and his associates have demonstrated that this type of ventricular fibrillation, produced by the digitalis drugs, differs from that caused by other agents such as electric shock, experimental coronary ligation or the use of various drugs. Oscillations produced by digitalis are slower and more regular and uniform[101] and are unaffected by sympatholytic agents.[102] In addition, digitalis does not lower the fibrillation threshold of the ventricle to other types of stimulation.[101] In nearly all cases death has followed intravenous rather than oral therapy.[103]

Although the offending digitalis preparations may be withdrawn at the onset of these various cardiac disorders, the abnormal rhythms may persist for as long as two weeks, because of the slow excretion of the drugs.[66, 80] It is known that similar arrhythmias may lead to irreversible changes in otherwise structurally normal hearts[104-107]; in an organically weakened heart further myocardial insufficiency may be promoted.[61] For this reason, physicians since Withering's time have searched for "the knowledge of a remedy to counteract its effects." This quest has, until relatively recently, been so barren that perusal of five standard American textbooks of medicine offers no suggestion other than withdrawal of the drug.[108-112] Recently several positive measures have been suggested for the treatment of the digitalis arrhythmias, and an attempt will be made in the concluding portion of this paper to review the history of this therapy.

(To be concluded)

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38061

PRESENTATION OF CASE

First admission. A thirty-three-year-old man was admitted to the hospital because of bronchiectasis. He had a chronic cough since he had had whooping cough at the age of three. From the age of seven he had repeated hospital admissions, and starting at the age of fifteen he had repeated episodes of pneumonia, usually in the winter. For many years he had raised 2 cupfuls of yellow foul-smelling sputum daily.

Two years before admission a routine serologic test for syphilis was positive, and arsenical and bismuth therapy had been given for a year and a half prior to entry.

Physical examination revealed mild clubbing of the fingers and rales at the left base, with absent tactile fremitus and decreased voice sounds.

The temperature was 98°F., the pulse 70 and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood revealed a hemoglobin of 90 per cent and a white-cell count of 11,950. A blood Hinton test was positive. The urine had a specific gravity of 1.014 and gave a ++ reaction for albumin. Bronchograms revealed bronchiectasis in the left lower lobe, the lingula of the left upper lobe and the right middle lobe, the process being most severe in the left lower lobe.

A left lower lobectomy and lingulectomy were performed. Postoperatively the patient developed an empyema; *B. subtilis* and nonhemolytic streptococci were cultured from this fluid. Closed drainage was instituted and sulfadiazine given. Despite good drainage a bronchopleural fistula developed. Over the subsequent five months the drainage became progressively less until it ceased, and his general well-being and strength increased.

Second admission (two years later). The patient was readmitted because of anorexia, weight loss, hemoptysis, fatigue and cough productive of copious yellow sputum.

Physical examination revealed dullness over the left lower thorax, with greatly diminished breath sounds. The trachea was deviated to the left and expansion of the left chest was limited.

The white-cell count was 15,500 and the hemoglobin 85 per cent. The urine gave a +++ reaction for albumin. A bronchogram revealed a pooling of lipiodol in the lower left chest cavity that suggested the possibility of a cavity in either the bronchi or the mediastinum. A sinus tract extended from the cavity to the left main bronchus.

A rib resection and drainage were performed.

Third admission (eight months later) because of persistent empyema and bronchopleural fistula. In the interval there had been a continuous drainage of yellow pus from the chest sinus. There was no improvement in his general condition, and he had gradually increasing dyspnea. He had had two bouts of pneumonia and several hemorrhages around the drainage tube. Physical examination was unchanged; the temperature, pulse, respirations and blood pressure were normal.

The urine gave a ++ reaction for albumin. Examination of the blood revealed a hemoglobin of 14.5 gm. and a white-cell count of 21,600, with 67 per cent neutrophils. The nonprotein nitrogen was 34 mg., the total protein 7.22 gm., the albumin 4.55 gm. and the globulin 2.67 gm. per 100 cc. *Staphylococcus aureus* and *E. coli* were cultured from the thoracic drainage. Blood and spinal-fluid Hinton and Wassermann tests were positive.

A Schede thoracoplasty with closure of the bronchopleural fistula was performed. A short time postoperatively a bronchocutaneous fistula appeared and

persisted. He improved gradually. He had received over 3,000,000 units of penicillin during this admission.

Fourth admission (three years later). The bronchocutaneous fistula remained open, draining for six months, and then closed spontaneously. Following this the patient had increasing difficulty in raising sputum, particularly at night, and sharp transient chest pain in the region of the chest wound, which had continued to drain.

Physical examination was essentially the same as on the previous admission. There was a draining chest sinus from which alpha-hemolytic streptococci were cultured. The blood pressure was 130 systolic, 80 diastolic. The vital capacity was 2 liters. A tuberculin test was positive. A urine with a specific gravity of 1.012 gave a + reaction for albumin. Roentgenograms of the chest revealed the heart and mediastinum to be displaced to the left. Bronchography revealed a relatively collapsed left upper lobe and, inferior and lateral to this, a suggestion of a sinus tract running into the thickened pleura.

A left-upper-lobe lobectomy was performed and after a stormy postoperative course, during which he was treated with penicillin and streptomycin, he improved gradually.

Final admission (two years later, at the age of forty-one). Shortly after discharge the patient noted dizziness and a staggering gait. Six months prior to admission he noted ankle edema and was given digitalis but stopped the medication of his own volition. Severe dyspnea and orthopnea developed; these and the edema were progressive. The dizziness and ataxia continued but were not progressive. For two to three months before entry there had been nocturia of 2 to 3 times. There had been no chills, fever or noticeable weight loss.

Shortly after the onset of the dizziness caloric tests had revealed hypofunctioning to completely inactive labyrinths, and neurologic examination was negative except for an unusual ataxia and inability to walk a straight line. No medication had helped these symptoms.

Physical examination revealed a thin, chronically ill-appearing man. There was decreased chest expansion and a depression of the left lateral chest. The left chest was dull throughout; the right showed bronchial breath sounds, coarse rhonchi and occasional rales. The neck veins were dilated in the upright position. There was a Grade I apical systolic murmur. A slightly tender liver was palpated 3.5 cm. below the costal margin. The spleen was not felt. There was ++++ edema of the lower extremities, extending up to the sacrum. Neurologic examination was negative; ataxia was present but could not be classified as to type.

The temperature was 98°F., the pulse 102 and the respirations 24. The blood pressure was 180 systolic, 105 diastolic.

The urine gave a ++++ reaction for albumin; the sediment contained an occasional hyaline cast and an occasional red and white cell. A concentration test showed maximum concentration to be 1.010. The twenty-four-hour urine excretion of albumin was 8.0 gm. per liter. A phenolsulfonphthalein test showed 11.25 per cent excretion in two hours. Examination of the blood revealed a white-cell count of 12,750, with 97 per cent neutrophils, a hemoglobin of 13.5 gm., a hematocrit of 41 per cent and a sedimentation rate of 1.5 mm. per minute. The nonprotein nitrogen was 52 mg., the total protein 5 gm., the fasting blood sugar 100 mg. and the total cholesterol 240 mg. per 100 cc.; the sodium was 137.5 milliequiv., the chloride 100 milliequiv. and the carbon dioxide 26 milliequiv. per liter. The prothrombin time was normal. A Congo red test revealed 58 per cent retention in the serum. The vital capacity was 1200 cc. Blood and spinal-fluid serologic tests were negative. A chest roentgenogram showed absence of the left lung, deviation of the trachea and heart to the left, scoliosis and a clear right lung field with some retained lipiodol. An intravenous pyelogram showed poor function bilaterally. In the retrograde pyelogram the kidneys appeared to be somewhat small, with some blunting of the calyces but without distortion of the renal pelves.

Digitalis and theocalcin were started and a 10-pound weight loss ensued over the subsequent two weeks. On the tenth day, which was the day following the retrograde pyelogram examination, he complained of pain in the left flank, accompanied by some tenderness; physical examination and laboratory findings were unchanged except for a tachycardia of 120 to 140. An electrocardiogram revealed an auricular rate of 60, a ventricular rate of 105, a QRS interval of 0.08 and right-axis deviation. The T waves were inverted in Leads 2, 3, AVF, V_4, V_5 and V_6; the R waves were high in Leads V_4, V_5 and V_6 and the S waves were deep in Leads V_2 and V_3. On the seventeenth day the respirations fell to 10 per minute, and the patient became drowsy. The blood pressure was 100 systolic, 50 diastolic. The nonprotein nitrogen was 100 mg. per 100 cc. and the sodium was 127 milliequiv., the chloride 85 milliequiv. and the carbon dioxide 30.7 milliequiv. per liter. The patient became anuric, lapsed into coma and died on the nineteenth day.

Differential Diagnosis

Dr. Jacob Lerman*: ". . . the sodium was 127 milliequiv., the chloride 85 milliequiv. and the carbon dioxide 30.7 milliequiv. per liter." I wonder about these chemical determinations. They may be explained by a combination of conditions. Obviously the patient was in renal failure, so a loss of sodium would be expected; he was uremic, so a lowering of the carbon dioxide would be expected, but

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he was having a diuresis and he also had pulmonary disease, both of which would tend to raise the carbon dioxide.

May I see the x-ray films?

DR. JAMES J. MCCORT: We have the films taken on the fourth admission subsequent to rib resection, left lower lobectomy and lingulectomy. There are coarse strands of increased density in the remainder of the left upper lobe, with compensatory emphysema of this lobe. Bronchography performed four days later discloses the presence of bronchiectasis in the remaining segments of the left upper lobe. A small sinus may be present communicating with the dilated left-upper-lobe bronchus. There is, in addition, evidence of bronchiectasis in the basal segments of the right lower lobe and possibly of the right middle lobe. Subsequent films, taken two years after the bronchogram and several months after the left upper lobectomy, show a further shift of the mediastinum to the left side, with dilatation of the trachea and compensatory emphysema of the right lung. There is patchy pneumonitis and persistent bronchiectasis in the basal segments of the right lower lobe. This situation remained relatively unchanged up to the period before death. The right lung is emphysematous, with bronchiectasis in the basal segments; a marked shift of the mediastinum results from surgical obliteration of the left thorax.

An intravenous pyelogram shows a slight delay in the excretion of the dye. Both kidneys are small, and there is a slight dilatation of the calyces and pelvis on the left. Retrograde studies made a few days later confirm the impression that the kidneys are small, and on the left side there is a slight hydronephrosis.

DR. LERMAN: Can you see any point of obstruction?

DR. MCCORT: There is no point of obstruction.

DR. LERMAN: I can assume, from the x-ray films, that there is persistence of infection in the right lung. There are obviously several systems involved here. The illness first started with pulmonary suppuration — I am given this information. Does one have to consider the various types of suppuration? Is it the ordinary type of bronchiectasis with complications — or is there, in addition or instead, a tuberculous infection? It is always difficult to rule out tuberculosis as a complicating factor in bronchiectasis, and the two may coexist. There is no indication in the protocol that tuberculosis was present. I am sure the various physicians looked for tuberculosis, and I think something would have been said about it if it had been present. I shall say that the patient did not have tuberculosis on the basis of the evidence available.

Could the patient have had any other kind of suppurative process? Could it have been a monilia infection that was so chronic and persistent, or a monilia infection complicating the original bronchiectasis? The yellow pus may be a clue to this, but I would like to see the statement that the organisms were isolated. The same would be true of actinomycosis. Although I might suspect actinomycosis, I cannot consider it as a possible complicating factor without some evidence such as isolation of the organisms.

I mention the fact that the history tells us that he had syphilis. The Hinton and Wassermann reactions finally became negative; I assume it was due to the treatment with penicillin. Although the damage to the labyrinth may be blamed on the past neurosyphilis, streptomycin could have done the same thing. I prefer the latter.

With long-standing pulmonary suppuration one of the complications I would expect is some form of kidney damage. Such kidney damage most commonly is one of two types, namely, amyloid disease and chronic glomerulonephritis. I do not know whether the evidence favors one or the other. The small shrunken kidney by x-ray examination certainly favors chronic glomerulonephritis; on the other hand, amyloid disease can do the same thing if the course is long enough. The Congo red test does not help me. The persistent albuminuria certainly favors amyloid disease; the late onset of hypertension also favors this. One can only infer that this patient had developed renal damage, either amyloid disease or chronic glomerulonephritis — probably the former. Another possibility, but not a likely one, is metastatic abscesses of the kidney, which, if extensive enough, would destroy most of the kidney; similarly, pyelonephritis should be considered. In these two conditions I would expect to find large kidneys by x-ray examination and a good deal of pus in the urine. Similarly, if there were tuberculous kidneys, I would expect somewhat enlarged kidneys, pyuria and other evidence of tuberculosis in the urine.

The third organ that was involved was the heart. Undoubtedly there was right-sided heart failure, resulting from a small pulmonary vital capacity. Finally, there was evidence of congestive heart failure — a large tender liver, rales in the lungs and peripheral edema.

It is difficult to account for the final episode, which occurred after the pyelogram. In this the respirations became shallow and few in number, and the patient went into collapse. There are various possibilities. It could have been due to cardiac failure, uremia or a combination of uremia and congestive heart failure. It could have been due to hemorrhage. It is possible that the patient could have hemorrhaged from the infected lung into the pleural cavity and collapsed as a result of this. A metastatic brain abscess, which is a common complication of pulmonary suppuration, could also cause collapse. Another possibility is emboli from an acute endocarditis, which may complicate pulmonary sup-

puration. It is not easy for me to explain the last episode. I assume that it was heart failure alone. The others are only suggestions.

In conclusion, I would say that this patient had pulmonary suppuration, hypertensive heart disease, right-sided heart failure and amyloid disease of the kidneys, with a second possibility of chronic glomerulonephritis.

A PHYSICIAN: Would you consider amyloid disease of the heart?

DR. LERMAN: I should have mentioned that. The congestive heart failure could be due to amyloid disease of the heart, but secondary amyloidosis does not often involve musculature in the same fashion as primary amyloidosis does.

A PHYSICIAN: Could a chronic glomerulonephritis go along for such a long time without red cells?

DR. LERMAN: He had no acute episode at any time. Many people have chronic glomerulonephritis without showing anything in the way of urinary changes except albuminuria and finally develop the terminal picture of chronic glomerulonephritis.

DR. BENJAMIN CASTLEMAN: I think the experience here has been that if there is chronic infection in the lung or somewhere else and if secondary involvement to that infection occurs in kidneys, it is more often pyelonephritis than chronic glomerulonephritis. Would you agree, Dr. King?

DR. DONALD S. KING: I think that is true.

CLINICAL DIAGNOSES

Chronic glomerulonephritis.
Uremia.
?Dissecting aneurysm, abdominal aorta.
?Renal artery occlusion.
Chronic bronchiectasis.
Hypertensive heart disease.
Latent syphilis.

DR. LERMAN'S DIAGNOSES

Pulmonary suppuration.
Congestive heart failure.
Amyloid disease of the kidney.
Hypertensive heart disease.

ANATOMICAL DIAGNOSES

Bronchiectasis.
Amyloidosis of kidney, severe.
Cardiac hypertrophy, right (cor pulmonale) and left (hypertension).
Pulmonary edema, acute.
Operations: lobectomies, left lower and upper.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed that the right lung had herniated slightly to the left side and did show evidence of mild bronchiectasis in the lower lobe. The heart weighed 500 gm., and there was not only right-ventricular hypertrophy due to pulmonary disease but also left-ventricular hypertrophy that may possibly have been related to the hypertension. The remaining lung was quite heavy, weighing 1100 gm.; it showed extensive pulmonary edema, and that was about all we could find to account for the acute episode.

The kidneys were small, about half the normal size, and somewhat scarred; on section they presented a glassy appearance quite characteristic of amyloid disease, which was confirmed microscopically. This was about the most extreme degree of amyloid disease I have seen; every glomerular tuft was completely or almost completely involved, and there was also amyloid infiltration of the interstitial tissues. It was surprising that the patient had lived so long with such severe renal failure. I suppose this degree of amyloid disease of the kidneys could produce secondary hypertension. There was a recent paper in the *New England Journal of Medicine** in which 40 cases of amyloid disease associated with hypertension were collected; usually hypertension does not follow amyloid disease of the kidney. Amyloid was also present in the adrenal gland, and there was a little in the liver. The spinal cord showed no known evidence of syphilis.

*Leard, S. E., and Jaques, W. E. Amyloid disease with hypertension: report of case and review of literature. *New Eng. J. Med.* 242:891-894, 1950.

CASE 38062

PRESENTATION OF CASE

First admission. A forty-seven-year-old man entered the hospital because of fatigue and dyspnea.

Seven months prior to entry the patient began to have a feeling of substernal and precordial constriction, brought on by walking or climbing stairs and relieved by four to five minutes of rest. After two weeks of these "attacks," while he was at rest he had the sudden onset of severe squeezing substernal and precordial pain that radiated to the left arm and lasted four to five hours. He was admitted to another hospital and a diagnosis of acute anterior myocardial infarction was made. He was treated in the hospital for five weeks by complete bed rest, sedatives and dicumarol. Following the initial subsidence of the chest pain he had no further pain, dyspnea, orthopnea or edema. At home he remained in bed for another three weeks, then was permitted gradually to become ambulant and finally returned to full activity two and a half months before admission. One and a half months before admission he noted excessive fatigue and began to have attacks of paroxysmal nocturnal dyspnea. One month prior to entry examination showed signs of right and left congestive heart failure and a loud musical systolic murmur and thrill that had not been noted before and was loud-

est in the third intercostal space along the left sternal border. An electrocardiogram at this time showed a pattern of left-bundle-branch block. For the four weeks prior to admission he remained at home, leading a bed-to-chair existence; in spite of this and digitalis and weekly injections of Mercuhydrin the marked fatigue and paroxysmal nocturnal dyspnea remained unchanged.

On physical examination the neck veins were slightly distended at 45°. There were a few scattered rales at the lung bases. The cardiac impulse was at the anterior axillary line. There was a protodiastolic gallop at the apex. The pulmonic second sound equaled the aortic. There was a Grade III musical systolic murmur with thrill heard all over the precordium but loudest in the fourth interspace just to the left of the sternum; this murmur varied with respiration and was loudest in the lying posi-

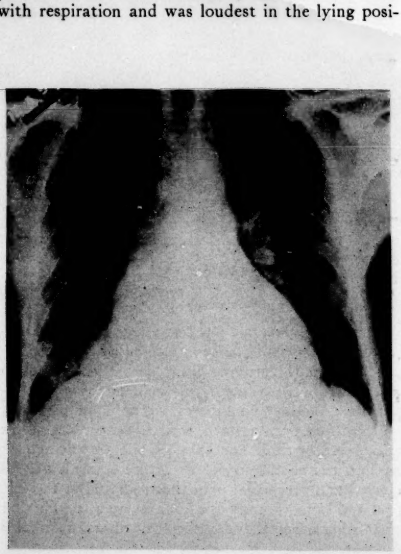

FIGURE 1.

tion. The liver edge was at the level of the umbilicus. There was no peripheral edema.

The temperature was 98.3°F., the pulse 112 and the respirations 24. The blood pressure was 115 systolic, 88 diastolic.

The urine had a specific gravity of 1.014 and gave a ++ reaction for albumin; the sediment contained many hyaline casts. Examination of the blood showed a white-cell count of 6100 and a hemoglobin of 15.5 gm. The nonprotein nitrogen was 32 mg. per 100 cc.; the sodium was 134.4 milliequiv., the chloride 100 milliequiv. and the carbon dioxide 25.1 milliequiv. per liter. A chest roentgenogram showed accentuated vascular markings, with prominence of the major pulmonary arteries. The heart was grossly enlarged; both right and left ventricles and, to some extent, the left atrium appeared to be enlarged. There was a small amount of fluid present in the right costophrenic sinus.

Treatment with a low-sodium diet, digitalis and mercurial diuretics resulted in a fifteen-pound weight loss and a great improvement in the dyspnea; the systolic murmur and thrill persisted, although it was no longer heard in the sitting position. He was discharged on the thirteenth day.

Final admission (eleven days later). In the interval the patient had done fairly well on digitalis and a low-sodium diet, as far as fluid retention was concerned. He had led a bed-to-chair existence. Ten days before admission he first noted blood-tinged sputum, and for the three days prior to entry he had brought up considerable amounts of grossly bloody sputum. There had been no chest pain or dyspnea. The day before admission he experienced a chilly sensation without any frank chills, and his temperature was 99.4°F.

On physical examination the neck veins were dilated and pulsating. There was dullness, increased tactile fremitus and bronchial breath sounds at the right lung base posteriorly. The heart, abdomen and extremities were unchanged from the previous admission.

The temperature was 102°F., the pulse 100 and the respirations 24. The blood pressure was 115 systolic, 80 diastolic.

The urine had a specific gravity of 1.020 and gave a ++ reaction for albumin; the sediment contained numerous hyaline and granular casts. Examination of the blood showed a hemoglobin of 15 gm. and a white-cell count of 12,900, with 82 per cent neutrophils. The bilirubin was 2.7 mg. direct and 4.4 mg. total per 100 cc. The prothrombin time was 21 seconds (normal, 14 seconds). A sputum culture grew abundant *Staphylococcus aureus* and a few nonhemolytic streptococci. The chest roentgenogram showed an oval area of increased density in the right base in addition to the findings noted on the previous admission (Fig. 1).

On the day of admission a bilateral common-femoral-vein interruption was performed and penicillin therapy was begun. The patient continued to bring up bloody sputum; the cardiac status remained unchanged. On the third day he became slightly jaundiced, and a loud friction rub appeared at the right base. The temperature was 103°F., the white-cell count was 9800 and the urine gave a + reaction for bile. Streptomycin therapy was started. He continued to be very ill and deteriorated rapidly.

On the fifth day the temperature was 102°F. On the sixth day the temperature was normal, but he was exhausted and complained of a chilly feeling, of cold hands and feet and of epigastric discomfort. There was slight increase in the venous congestion in the neck and in the size of the liver. The blood pressure became unobtainable and the pulse rapid, and he died.

Differential Diagnosis

Dr. Richard J. Clark*: I should like to know more about the past history of this patient. Nothing was said about previous cardiac findings, symptoms or blood-pressure level; being told nothing, I must assume that they were within normal limits.

Dr. Conger Williams: They were; he had been examined by his family physician on a number of occasions before his first hospital admission. The murmur had never been heard. He had apparently been well prior to this.

Dr. Clark: The patient gave a history of typical angina pectoris some nine months before entry that went on for a period of approximately two weeks; then he developed what was undoubtedly an acute myocardial infarction. There is little point in debating this diagnosis. The electrocardiogram was reported as indicating an anterior infarction, and I think I should accept this diagnosis at its face value. Then this patient had a rather prolonged convalescence, which by history was uneventful. Four months from the onset he returned to work, and from the history we may judge that he was in good condition. Suddenly, after he had been at work for approximately a month's time, he developed signs of myocardial insufficiency with nocturnal dyspnea. Two weeks later an examination gave evidence of right- and left-sided congestive heart failure and revealed a systolic murmur and thrill to the left of the sternum. It is on the basis of this murmur that the crux of our discussion rests. In the meantime there had been no history of further chest pain. From this point on he had rather persistent and resistant congestive heart failure. The electrocardiogram was reported as showing bundle-branch block. I judge that this represented a rather striking change from the pattern previously noted when it was said to have shown anterior infarction, but I cannot infer too much from this.

The patient was hospitalized, and the findings previously reported were confirmed. Now the murmur was described as being in the fourth intercostal space and of about Grade III intensity associated with a thrill. The blood pressure, reported for the first time, was essentially normal. He improved under treatment, having a reasonably good diuresis. There was some decrease in the intensity of the systolic murmur so that it was no longer audible in the sitting position. X-ray films were taken; we might look at them now.

Dr. Stanley M. Wyman: There is nothing to add to the description in the protocol. The heart shadow is definitely enlarged. There is engorgement of main pulmonary arterial shadows, extending well out into the lung fields. There is a small quantity of fluid in the right pleural space (Fig. 1). As nearly as one can determine, the enlargement of the heart is rather general, probably involving both left and right ventricles; in the lateral view there is a suggestion that the left auricle is full.

Dr. Clark: We might pause at this point and try to decide what had been going on prior to and during this first admission to the hospital. I shall assume that this man did have a myocardial infarction. He apparently recovered quite satisfactorily, and then in four to five months something suddenly happened that precipitated acute failure and was associated with the development of this striking systolic murmur and thrill. What could happen under these circumstances to give findings of this type? In the first place, was this an organic murmur or was it a so-called functional murmur? There was evidence that the murmur was louder when the patient was in the recumbent position; after the congestive heart failure had been treated, the murmur was said to have disappeared in the sitting position and to have been present only in the recumbent position, but the thrill still persisted in the recumbent position. That is a rather unusual situation. A murmur that is variable to this degree I would ordinarily consider a functional murmur, but when it persists with sufficient intensity, even in the recumbent position alone, to be associated with a distant thrill, I am not willing to accept it as a functional murmur; I shall assume it was a murmur of organic origin.

What could produce a murmur of this type? Pulmonary stenosis may conceivably produce a murmur, as described, although the murmur was somewhat low in location for such a lesion. What could suddenly produce a pulmonary stenosis and this sort of picture? I cannot conceive of anything short of massive blocking of the main pulmonary artery, and certainly such a condition would not permit survival for weeks, as in this case.

Stenosis of the aortic valve can give strange and unexpected findings on auscultation. The murmur may be heard almost entirely at the apex and not at the base or even between the two areas, but when there is an associated thrill this is usually found in the aortic area. I can conceive of nothing in the aortic valve that would occur suddenly and give a systolic murmur and thrill.

What else could have happened? Occasionally rupture of a papillary muscle may occur after myocardial infarction. With this the patient develops a sudden loud systolic murmur, but the mur-

*Assistant physician, Massachusetts General Hospital.

mur is described most commonly as occurring at the apex. In the relatively small number of such cases reported, the patients have usually died within a matter of minutes or hours.

The murmur and thrill as described in this case fit well with the picture of a ventricular septal defect, which we see usually as the congenital type. Could this represent a septal defect? Rupture of the ventricular septum has been reported as a relatively rare complication of myocardial infarction. Bickerman and Irons[1] reported one case that was diagnosed during life and gathered from the literature some 60 cases of rupture of the ventricular septum after myocardial infarction. The diagnosis is made on the basis of the murmur and thrill, the location and nature of which are similar to those seen in this particular case. The course after rupture of the ventricular septum is usually rapidly downhill, with increasing and resistant congestive heart failure and possibly with increasing angina pectoris. The majority of these patients have died within a matter of hours or a relatively few days; however, several cases have been reported with a longer period of survival; in fact, there was one man aged forty-five who was reported as surviving for a period of five years after rupture of the ventricular septum.[2]

When does rupture of the heart muscle or of the septum occur in relation to myocardial infarction? It is usually within the first two weeks; that is the point that bothers me most about this particular case. The time relation of the appearance of the murmur is wrong. On the other hand, this man had rather sudden difficulty with nocturnal dyspnea two weeks before he was seen with the murmur; it is possible that he may then have had an infarction of the septum that did not produce pain and was not diagnosed. Possibly the change in the electrocardiogram from a fairly typical anterior-infarction pattern to that of bundle-branch block might have occurred with this. Although the somewhat atypical features of the murmur still disturb me, I shall hold to a rupture of the interventricular septum as the most likely of various possibilities.

The patient went home from the hospital and did fairly well as far as the congestive heart failure was concerned, but he returned to the hospital eleven days later with what was a very typical picture of pulmonary infarction. Is there anything to add from the x-ray films?

DR. WYMAN: No; the infarct, as described, is quite well seen in the right cardiophrenic angle. I think it may lie at the base of the lower lobe.

DR. CLARK: The radiologists seem to agree that this was a pulmonary infarction. The assumption was made that there was thrombosis in the leg veins, and the leg veins were tied. Nothing is said about dicumarol therapy. I would be interested to know if this was considered. The patient had an increased prothrombin time; perhaps dicumarol was withheld on the basis of this elevation. If he were to have had dicumarol, it certainly should have been in small and guarded doses, but generally in a patient with potential endocardial thrombi, as in this case, I would favor dicumarol regardless of femoral ligation.

There was evidence that this patient had infection; I would suspect that this was in the lung secondary to the pulmonary infarction. He subsequently developed jaundice of a mild degree. We know that after pulmonary infarction we may see jaundice that is on a hemolytic basis, in a man who had congestive failure for some time; he undoubtedly had poor liver function and congestion in this organ.

In the course of the next several days this patient went rapidly downhill, with increasing congestive heart failure and evidence of infection. My diagnoses are old myocardial infarction, anterior and septal, with probable rupture of the interventricular septum, congestive heart failure and pulmonary infarction, which may have resulted from either phlebitis of the leg or endocardial thrombi.

DR. WILLIAMS: There is one point I would like to clear up with Dr. Clark. This murmur appeared during the first hospital admission a week to ten days after the onset of pain.

DR. CLARK: With the first infarction?

DR. WILLIAMS: Yes; therefore we thought, as you did, that he undoubtedly had a ruptured interventricular septum. In addition to the murmur, we thought another strong argument for this was the rapid onset of congestive heart failure in a young man with his first coronary attack, although he had gotten over the episode quite well. Then suddenly he went into congestive heart failure, more rapidly than is usual in a young person who has had his first coronary attack. Another diagnosis considered was that of subacute bacterial endo-

carditis on the basis of a ruptured interventricular septum. If he had that, we would then expect him to start out with pulmonary emboli rather than peripheral emboli; in congenital interventricular defect complicated by subacute bacterial endocarditis, emboli go to the lungs rather than to the periphery, and one might expect the same rule to hold in the case of a ruptured septum of long duration.

Dr. Clark: What about the development of pulmonary emboli and thrombi in the legs in the presence of liver disease that is producing as high a prothrombin time as this? Is that somewhat surprising to you, or do you think that the elevation in the prothrombin time came after he had the pulmonary infarction?

Dr. Williams: We do not know; the first blood spitting came at least ten days prior to hospital admission, so the patient may have had a large pulmonary embolus before he came in. It made the whole case very difficult. I thought that although he was quite ill I would rather gamble on the venous ligation than on dicumarol at that time. We did not know what was going on; we thought that he might have had subacute bacterial endocarditis. In addition to the other things, it was evident that he had an infection. The control prothrombin determination was 38 per cent of normal, raising the question of liver disease. He was seen by Dr. Thomas Paine, who thought that he possibly had a staphylococcus pneumonia in addition to pulmonary infarcts.

Dr. Clark: Dr. Wyman, would you consider that these x-ray findings are consistent with a ventricular septal defect — that the overloading of the pulmonary system might be due to some degree of left-to-right shunting?

Dr. Wyman: I could not detect the difference, Dr. Clark, between that and ordinary congestive heart failure or, perhaps, the result of coronary occlusion. I agree with you, however, that it is an unusual picture for a man of this age to show so much pulmonary congestion from a simple coronary occlusion.

Clinical Diagnoses

Coronary heart disease.
Old myocardial infarction.
Ruptured interventricular septum.
Congestive heart failure.

Dr. Clark's Diagnoses

Old myocardial infarction, anterior and septal.
Ruptured interventricular septum.
Congestive heart failure.
Pulmonary infarction with secondary infection.

Anatomical Diagnoses

Myocardial infarction.
Mural thrombus, left ventricle, producing aortic stenosis.
Pulmonary infarcts.

Pathological Discussion

Dr. Castleman: At autopsy the heart was enlarged, weighing a little under 500 gm. When the left chamber was opened it was apparent that it was almost all infarcted; the only part that was not infarcted was the posterior wall, so certainly one half to two thirds of the heart was involved (Fig. 2). Superimposed on the infarction were mural thrombi; one tremendous one was implanted just under the aortic valve. The aortic valve was normal. There was no septal perforation. We have interpreted this thrombus as large enough and close enough to the aortic valve so that during life it protruded into the aortic orifice sufficiently to produce stenosis and the murmur and thrill. The thrombus itself extended

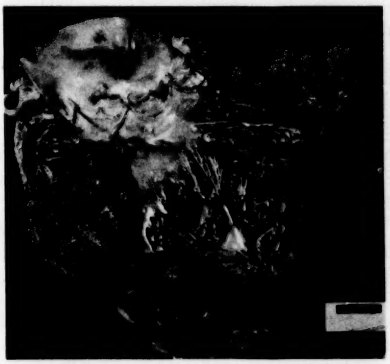

Figure 2.

higher up than it was implanted. I do not recall ever seeing anything just like this before as a cause of aortic stenosis, but I believe it adequately explains why the murmur was heard best when the patient was lying down.

DR. CLARK: Was there thrombosis on the right side of the septum as well as the left?

DR. CASTLEMAN: No; there was none on the right side. There was an old occlusion in the anterior descending branch of the left but no evidence of anything recent. There were two infarcts in the lung, a large one involving almost the entire right lower lobe and a smaller one in the costophrenic angle of the left lower lobe. There was evidence of moderate congestive heart failure.

DR. CLARK: Did the liver show anything unusual?

DR. CASTLEMAN: Just slight central congestion. The leg veins, both superficial and deep femorals, had been tied and there were no thrombi on either side of the ties. We did find mural thrombi in the right auricular appendage, which probably was the source of the pulmonary infarcts.

DR. CLARK: You are convinced that there were no thrombi in the legs?

DR. CASTLEMAN: None were found at operation, and we found none at autopsy in the sites where they had been tied. I would think that in this particular case the emboli probably came from the right-auricular appendage.

DR. CLARK: This is of interest in conjunction with the case that was just discussed at Medical Grand Rounds. There Dr. Robert Linton stated that he would tie veins in any case in which pulmonary infarction had occurred. Our case certainly gives further argument for the additional use of dicumarol in cardiac patients with pulmonary infarction, although I can understand very well why the attending physicians were guarded about its employment in this particular situation.

DR. WILLIAMS: As long as one cannot tell where emboli are coming from and as long as the use of dicumarol has an additional hazard, I still think one might decide to tie these veins in such a situation. The thing that bothered us about the diagnosis of ventricular septal defect, just as it did Dr. Clark, was the variability of the murmur. None of us had ever seen a murmur as variable as this in any kind of septal defect. It was a very impressive murmur.

DR. ERNEST CRAIGE: Do you know if the patient was given adequate dosages of dicumarol when he was seen with the chest pain?

DR. WILLIAMS: I think he was.

DR. CASTLEMAN: That is a little surprising; you would not expect the formation of so large a thrombus, unless it developed after the dicumarol was stopped.

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JOURNAL OF THE STUDENT AMERICAN MEDICAL ASSOCIATION

The first issue of the *Journal of the Student American Medical Association*, at the moment the youngest of an almost incredibly large family of publications devoted to medicine, has put in its awaited appearance. Almost verdant in its green and white cover, this is the first of an annual crop of nine issues, which will appear at monthly intervals except from June to October. Important in its contents is a guest editorial by Dr. Austin Smith, editor of the *Journal of the American Medical Association*, emphasizing the close relations that should exist between the Student American Medical Association and what may be considered its parent organization.

Various departments in the new journal are designed to meet the special needs of students. Among these are a Washington wire to answer questions on Federal legislation, government regulations and the mechanics of legislative processes; a newsletter; letters to the editor; book reviews; and a list of S. A. M. A. academic societies. Three scientific papers are included, of which two are reviews by students. There are in addition five socioeconomic articles, with an illustrated story on the University of Illinois College of Medicine as leader.

Published in Chicago for the student association by the American Medical Association, the journal is under the lay executive editorship of Russell F. Staudacher, with Walter H. Kemp of Chicago as managing editor and Philip Corso, a fourth-year student at Tufts College Medical School, as student editor.

The attractive format is rather that of a trade or other lay magazine than of a scientific run-of-the-mill medical journal, — as, indeed, it should be, to serve its useful purpose, — with more than the usual number of illustrations and with the advertisements infused throughout the text.

The principal objectives of the Student American Medical Association, — developed under and guided by the experienced hand of the American Medical Association, — are to indoctrinate students early in their novitiate in the ethical standards and the internal and external relations of their profession, and to interest them in the organizational means through which these relations are intended to achieve uniformity.

One danger inherent in an organization so developed will of course be assiduously avoided — that of excessive paternalism. These young men, so soon to become the independently thinking physicians of the country, may have certain patterns of thought and action demonstrated to them, but also they will be encouraged to view medicine and its problems through their own eyes. No generation has done so well in its conduct of the world's affairs that it dare recommend its own methods to its successors; all it can do is to point to its achievements and warn against its failures. Thought provocation is one thing, but thought control, of which

there has been far too much in the last 20,000 years, is another.

The generation in action can only implore the one in training to guard the freedom of the future and perpetuate as few as may be of the errors of the past. It is a charge on today's leaders that the younger men who accept their guidance shall be left free to develop their own opinions and shall be protected against the risk of being suckled in any creeds of unrevised traditionalism.

ANTIBIOTICS AND BLOOD COAGULATION

Since 1945, when Moldavsky and his co-workers[1] first reported a lowering of the clotting and bleeding time in patients receiving penicillin, considerable interest has been shown in the possibility implied in this and later reports that the use of penicillin and other antibiotics may have increased the occurrence of thrombotic phenomena. About two years ago Long,[2] in a letter to the editor of the *Journal of the American Medical Association*, commented on a newspaper report of a paper by Alton Ochsner. In this report the latter is cited as having described an increased occurrence of fatal cases of pulmonary embolism as probably due to the increased coagulability of the blood resulting from the routine administration of antibiotics to all hospital patients. Ochsner is quoted as having reinforced his thesis by citing some experiments that demonstrated that antibiotics shortened the coagulation time in man and in animals.

The possible effect that such a statement may have when it is seized on by antivivisectionists and other professional baiters of physicians and medical schools was well illustrated in Long's letter. In spite of this, there has certainly been no diminution in the number of physicians who prescribe antibiotics or in the amounts prescribed. In fact, the reverse is true; the number and amounts of antibiotics being prescribed have increased steadily, as evidenced by the progressive rise in the production and sales of these agents. Indeed, it is most unlikely that even Dr. Ochsner and his associates have gone so far as to give up these life-saving agents or even to reduce appreciably the amounts that they give their patients.

Obviously, this increased use of antibiotics is not, as the leaders of the antivivisectionists would have our legislators believe, due to the fact that many people now die unnecessarily as a result of the use of these drugs. All of us know beyond peradventure that the exact opposite is true — namely, that many are now alive as a result of the use of antibiotics who would otherwise have long since been dead. Furthermore, although it is undoubtedly true that deaths from thromboses and embolism still occur, there is no acceptable evidence that such deaths are nearly as frequent as they were before the days of antibiotics. Nor is there any indication whatever that the administration of antibiotics is responsible for these or other thromboses and emboli, except perhaps for the relatively few cases in which local thromboses occur at the site of intravenous injections — and these are rarely if ever the cause of fatal emboli.

The literature on the effects of antibiotics (and of many other drugs as well) on blood coagulation and relative phenomena has recently been succinctly reviewed by Seegers.[3] In this review the contradictory reports on the effects of antibiotics on blood coagulation have been presented. Seegers summarized the findings on the in-vivo effects of penicillin as indicating that this antibiotic causes no major change in the coagulation mechanism when used in a reasonable range of dosage. In-vitro concentrations up to 500 units per cc. were found to produce no change, whereas concentrations of over 3000 units per cc. caused retarded clot formation and retraction. With respect to aureomycin, most of the reports quoted indicated that there was no significant alteration in coagulation time, prothrombin time, bleeding time or the in-vitro heparin-tolerance test. One worker, however, is quoted as finding a markedly shortened coagulation time, whereas another maintains that coagulation time is actually prolonged by aureomycin. The evidence pro and con has also been reviewed recently by Macht.[4]

Seegers summed up the evidence as follows: "Unfortunately, our knowledge of the effects produced by antibiotics on the coagulation process has

progressed very little. Most of the reports in favor of an effect do not convince the critical reader. . . . The matter warrants more thorough investigation."

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BENJAMIN RUSH IN EDINBURGH

THE Autumn number of the *University of Edinburgh Journal* for 1950 contains an article of lasting interest to anyone who may be concerned with the history of American medicine. It is the MacArthur Post-Graduate Lecture delivered at the University of Edinburgh Faculty of Medicine on July 18, 1950, by George W. Corner, M.D., director of the Department of Embryology of the Carnegie Institution of Washington. The subject is "Benjamin Rush's Student Days in Edinburgh, and What Came of Them."

Young Rush, arriving in Edinburgh on November 3, 1766, at the age of twenty-one, had already graduated as a bachelor of arts from the College of New Jersey, now Princeton University, after which preliminary education he had served a five-year apprenticeship with a Philadelphia physician. In order to reach his destination he had spent two months on the Atlantic Ocean and nearly a week on the road from Liverpool. The shrine was worth the pilgrimage, however, for Scotland was then at the very peak of her leadership in medical education. Alexander Monro (*secundus*) was professor of anatomy at Edinburgh; William Cullen, who exerted perhaps the greatest influence over the youthful colonial, occupied the chair of medicine; and Joseph Black and John Gregory were, respectively, professors of chemistry and medicine and of the practice of physic.

Although no less than fourteen other American medical students were currently availing themselves of the educational opportunities to be found at Edinburgh, two in particular who had barely preceded Rush are worthy of mention. These are John Morgan and William Shippen, who were soon to establish the first school of medicine in America, at Philadelphia, where Rush was later to join them as professor of chemistry.

Rush, as a strict Presbyterian, was approved of in Edinburgh, and he in turn approved of the city. As he later wrote in his *Travels Through Life*:

> During my residence in Edinburgh I was often struck in observing the moral order which prevailed among all classes of people. Silence pervaded the streets of that great city after 10 o'clock at night. The churches were filled on Sundays. I never saw a pack of cards in either a public or private house. . . .This universal morality was not accidental. It was the effect of the parochial instructions of the clergy, who were at that time a regular and conscientious body of men.

The first entry in his student journal gives further evidence of the seriousness of purpose of the young Philadelphian and his appraisal of the value of foreign travel:

> In the following Journal I am resolved to confine myself chiefly to observations of Men and Manners. This is the most fruitful source of reflection and improvement. A man who suffers his Attention to be occupied while Abroad only in Surveying grand Buildings and in Attending places of public Entertainment defeats the design of travelling, and is less wise when he returns to his Native Country than when he left it. I am determined to cultivate the Acquaintance of Men of Learning and Virtue wherever I go, and shall endeavour to find out the Customs and Manners of the People with whom I may be called to associate.

One especial influence that effected a change in Rush's whole social and political outlook was that of a fellow student, John Bostock. Recent ancestors of each of the young men had been company commanders in Cromwell's army, and on the basis of this discovery Bostock "now opened his mind fully to me, and declared himself to be an advocate for the Republican principles for which our ancestors had fought."

> Never before had I heard the authority of Kings called in question. I had been taught to consider them nearly as essential to political order as the Sun is to the order of our Solar System. For the first moment in my life I now exercised my reason upon the subject of government. I renounced the prejudices of my education upon it; and from that time to the present all my reading, observations and reflexions have tended more and more to shew the absurdity of hereditary power, and to prove that no form of government can be rational but that which is derived from the Suffrages of the people who are the subjects of it.

Thus there was born in Edinburgh the Rush who was later to become a member of the Continental Congress and a signer of the Declaration of Independence.

DOUBLE VISION

Not only is it desirable in the flowery meadows of romance to have occasionally two hearts that beat as one; in the practical field of optics it is a mandatory matter for the majority of persons to possess two eyes that see in perfect harmony. In other words, for the proper perception of space and distance stereoscopic vision is highly desirable if not essential.

Failure of the eyes to blend their images and produce a single three-dimensional picture results in double vision, long associated in the otherwise normal person almost exclusively with the euphoria that accompanies the bacchanalian revel. There is a certain sense of security, possibly false, that may accompany this toxic manifestation, for it is apparently easier to walk between two chalk lines than on top of a single one, though not with four feet.

A timely warning now comes from the Department of Physiology of the University of Chicago that other factors contributing to eye fatigue may produce the same result. Drowsiness as well as drinking can create double vision, with its effects most marked in those bleak hours between midnight and morning familiarly known as the graveyard, or perhaps more appropriately the gravy-eyed watch.

These are the hours of the twenty-four that are marked by a relatively high rate of automobile accidents, the outcome, possibly, of unhappy attempts to drive between two trailer trucks where only one exists. On the basis of these observations drivers are advised to pull off the road in the early morning hours, — but not between two telegraph poles, — and wait for more normal vision to return.

The idea that it is very improper for females to employ male dentists, is beginning, so it is said, to have advocates. Where is the refinement of civilization to end?

Boston M. & S. J., *February 11, 1852*

BOOK REVIEW

Physicians' Federal Income Tax Guide: For the preparation of 1951 returns and 1952 estimates. By Hugh J. Campbell and James B. Liberman. 4°, paper, 112 pp. Great Neck, New York: Doniger & Raughley, Inc., 1952. $2.50.

This valuable handbook supplies to the physician and surgeon all the information necessary for properly filling out actual and estimated income-tax forms as required by the Government. Nontaxable income and allowable professional deductions are tabulated in simple form. The various items in Form 1040 are discussed at length and in the order in which they appear in the form. There is a good index, and the printing is well done. The book is an essential tool for everyone practicing medicine.

NOTICES

AMERICAN ASSOCIATION OF THE HISTORY OF MEDICINE

In order to stimulate interest and research in medical history among students of the medical schools of the United States and Canada, the American Association of the History of Medicine has established a medal to be granted annually to the author of the best student essay submitted to the association.

The medal has been named in honor of William Osler, who more than any other academic teacher succeeded in creating among students enthusiasm for the history of medicine.

The association will consider unpublished essays by men or women who were students in schools of medicine and had not yet obtained their doctor's degree at the time the essay was written. Essays that are the result of original research will be given preference, but the association will also consider essays that, even if not the result of original research, show an unusual appreciation and understanding of historical problems.

Essays must be sent before April 15, 1952, to Benjamin Spector, M.D., Tufts College Medical School, 136 Harrison Avenue, Boston 11, Mass.

SOUTH END MEDICAL CLUB

The next luncheon-meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, February 19, at noon. The speaker will be Dr. Louis Weinstein, chief of the Infectious Disease Service, Massachusetts Memorial Hospitals. His subject will be "The Chemotherapy of Infectious Diseases."

All physicians are invited to attend.

GREATER BOSTON MEDICAL SOCIETY

The next meeting of the Greater Boston Medical Society will take place on Wednesday, February 13, at 8:15 p.m., in the auditorium of the Beth Israel Hospital.

Four phases of current work at the Beth Israel Hospital will be presented. Dr. Edward Frank will speak on "Recent Experiences with the Artificial Kidney"; Dr. Howard Frank, on "The Use of Venograms in Recurrent Varicose Ulcer"; Dr. Benjamin Alexander, on "Management of Certain Hemorrhagic Disorders"; and Dr. A. Stone Freedberg, on "Clinical Usefulness of Radioactive Iodine."

NATIONAL CANCER CONFERENCE

The Second National Cancer Conference, sponsored by the American Cancer Society, the National Cancer Institute and the American Association for Cancer Research, will be held at the Netherland Plaza Hotel, Cincinnati, Ohio, March 3 to 5.

Further information concerning the program may be obtained from the Professional Education Section, American Cancer Society, Incorporated, 47 Beaver Street, New York 4, N. Y.

SOCIETY MEETINGS AND CONFERENCES

February 9–27. Springfield Hospital. Page 204, issue of January 31.

February 11 and 12. American College of Surgeons. Page 160, issue of January 21.

February 12. Springfield Academy of Medicine. Page 204, issue of January 31.

February 12–26. Boston City Hospital House Officers' Association. Page 160, issue of January 24.

February 13. Greater Boston Medical Society. Notice above.

February 13. Boston Society of Biologists. Page 204, issue of January 31.

February 13–March 26. Lahey Clinic Fellowship Teaching Program. Page 160, issue of January 24.

February 14. Cancer of the Breast. Dr. Ernest M. Daland. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

February 18 and 19. American College of Surgeons. Page 203, issue of January 31.

February 19 South End Medical Club. Notice above.

(*Notices concluded on page xvii*)